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MODERN MEDICINE

ITS THEORY AND PRACTICE

IN ORIGINAL CONTRIBUTIONS BY AMERICAN AND FOREIGN AUTHORS

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VOLUME IV

DISEASES OF THE CIRCULATORY SYSTEM—DISEASES OF THE BLOOD—DISEASES OF THE LYMPHATIC SYSTEM—DISEASES OF THE DUCTLESS GLANDS—VASOMOTOR AND TROPHIC DISORDERS

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PART I.

DISEASES OF THE CIRCULATORY SYSTEM.

CHAPTER I.

GENERAL CONSIDERATIONS IN CARDIOVASCULAR DISEASE.

By CHARLES F. HOOVER, M.D.

Introduction.—The problem for a physician to solve when confronted with a case of circulatory disease is, Which of the many factors in the maintenance of the circulation are at fault? Briefly stated, he must determine if there is a faulty distribution of the blood, viz., in the peripheral vessels, in the splanchnic area or in the pulmonary circulation; if the pure hydraulics of the circulation are maintained and if its accomplishment is fulfilled without an expenditure of more than a normal amount of work by the heart. Some of these problems have their solution in phenomena purely physiological, some pathological, and some are still in the realm of theoretical speculation. Where physiology and pathology fail, the diagnostician can appeal only to recorded clinical symptomatology.

The factors in the normal maintenance of the circulation are: an efficient myocardium with a sound directing innervation, efficient and unobstructing valves at the atrioventricular and arterial orifices, an aorta and branches of suitable caliber with elastic walls. Furthermore, the aortic system must fade into small branches with walls of given elasticity and vasomotor tone. There must be an unhindered centripetal flow of blood in the veins, supported by the vasomotor tone of the venous walls, the valves, and contraction of the skeletal muscles.

We have not only the propelling agencies to consider, but also the aspirating forces in the thorax. These are the normal negative tension in the pleural cavity and the inspiratory effort in breathing. Another aspirating force is from the diastole of the heart, which may have an importance equal to the systole; in some instances of pericardial and myocardial disease a faulty diastole may be the chief cause of trouble. The problems mentioned have to do largely with the systemic circulation and most circulatory disturbances occur in this distribution, but

the right ventricle and the pulmonary vessels may be the seat of trouble which is primarily in the pulmonary arteries or induced secondarily from diseases of the lung.

This discussion will be restricted to the consideration of a few of the physiological aspects of diseases of the circulation, and an attempt to show that this view of cardiovascular disease may engage the attention of a physician without the aid of any so-called instruments of precision.

Distribution of Blood.—If the equable distribution of blood be disturbed, the cause must be in the central pumping organ or somewhere in the systemic or pulmonary vascular system. The most direct method of determining the site and character of the defect is to locate, if possible, a point where massing of the blood occurs. Massing of the blood at the proximal side of a lesion is often the source of symptoms which most attract the patient's attention, viz., cough and dyspnœa from pulmonary stasis, when the left side of the heart is the seat of trouble; or discomfort in the hepatic region from stasis in the liver when the right heart is no longer able to propel a sufficient mass of blood. When propulsion of blood in the distal circulation is impaired, evidences of the character above mentioned are notably absent and the mass of blood accumulates in the splanchnic circulation, as seen in shock, depressor nerve influences, and vasomotor exhaustion in the terminal stages of infectious diseases. The same occurs in instances of reflex vasomotor dilatation in the abdominal vessels.

If there is impairment in *mass movement* of the blood, either of a positive or negative character, the first duty of the physician is to seek some evidences of an excessive accumulation which may be under increased pressure or under diminished resistance of the sustaining vascular walls. Dilatation of the splanchnic vesels is a common instance of the last-named condition. Stasis in the pulmonary circulation is by far the most common evidence of excessive accumulation of blood when there is any pure hydraulic distress in the cardiovascular system. Primary disease of the pulmonary arterial system is rare. Although the branches of the pulmonary artery have an abundant supply of muscular tissue in their walls, there is a very feeble vasomotor nerve supply. In the pulmonary circulation there is not the same demand for widely varying degrees of resistance in certain regions of supply, as in the aortic system. The respiratory function at any given time is the same in all parts of the lung; so there is no need of any device which will increase the supply to one portion of the lung over that of another part. What rôle vasomotor impulse plays in the pulmonary circulation is unsolved. Experimentally, no one has succeeded in demonstrating a rise of pressure from vasoconstriction of more than about 20 per cent. of the normal pulmonary arterial pressure.

Some French physicians have reported a number of cases interpreted as vasomotor spasm of the pulmonary arteries caused by reflex stimuli from the abdominal viscera, chiefly the liver. It is a notable fact in these accounts that they improved under treatment which would be suitable for myocardial insufficiency from any source. The writer has not met with an instance which would bear such an interpretation.

Experimentally, three-fourths of the pulmonary arterial branches can be tied off before there will be any evidences of insufficiency from the tricuspid valve or any diminution in the amount of blood delivered to the left auricle.

Should the left ventricle fail to propel an amount of blood equal to that supplied from the right ventricle, there is directly an increase of pressure in the left auricle and pulmonary veins and finally in the pulmonary arteries. Von Basch described this state of the pulmonary circulation as the rigid and distended lung. He conceived pulmonary stasis as an erectile state of the entire pulmonary vascular system which caused an increase in volume of the infundibula and impaired the elastic excursion of the lung, a state which could be legitimately described as a red emphysema in contradistinction to white emphysema, which is the atrophic form with a flaccid and anemic lung. In the lung of vascular stasis, dilated and tortuous vessels encroach on the air spaces, and secondary changes in the capillary walls, infundibular walls, and bronchi are the factors of dyspnœa so far as the lung itself (independently of slowing of the blood stream) is concerned. Kraus showed, by direct observation on patients with severe cardiac lesions, that the respiratory insufficiency of pulmonary vascular stasis is not due to a mechanical defect in the lung. By analyses of the inspired and expired air of patients suffering from cardiac lesions the amount of air entering and leaving the lungs was shown to be the same as in healthy persons. There was not the same exchange of oxygen for carbonic acid as in normal conditions. Although there was an excessive ventilation of the lungs, there was a diminished ventilation of the blood due to the slowing of the blood current and the pathological changes in the lung.

In pulmonary stasis we find the lower borders of the lungs occupying a lower position in the thorax than during the periods of fair compensation, but this increased volume of the lung is due to increase of volume which attends the emphysema of an accompanying bronchitis and increased effort at breathing. The increase in vascular volume of the lung takes place very largely at the expense of the infundibular air spaces. Although von Basch's conception of pulmonary stasis found many followers and the theory in itself was a very attractive one, it is not in accord with either pathological or physiological demonstrations. Obstruction to the pulmonary blood stream either from increased resistance in the branches of the pulmonary arteries or from insufficiency of the left heart becomes apparent through diffuse bronchitis or pulmonary œdema and evidences of increased tension in the pulmonary artery. Œdema of the lungs is not an invariable accompaniment of a high degree of pulmonary stasis. In myocarditis accompanying acute infectious diseases, the writer has seen primary dilatation of the left ventricle followed in thirty-six hours by great dilatation of the right ventricle. The tension in the pulmonary artery was so high that the pulmonary valves were not able to sustain the diastolic pressure in the pulmonary artery and a loud diastolic murmur appeared at the pulmonary orifice. Myocarditis of the right conus arteriosus may be a factor also in causing the diastolic murmur. The murmur and evidences of high

tension in the pulmonary artery disappeared promptly with recovery of the myocardium. During this period of cardiac failure there was not an adventitious sound audible over the lungs. Stasis under high tension is not the sole requisite for œdema of the lungs.

A strong diastolic impact over the second intercostal space and third rib at the left border of the sternum is not sufficient proof of high tension in the pulmonary artery. This impact may be present on account of proximity of the conus arteriosus to the thoracic wall, which occurs when the left lung is retracted or the conus arteriosus dilated.

In addition to evidence concerning the size and functions of the conus arteriosus, right ventricle, and auricle, other evidences of insufficiency of the right ventricle commonly present are signs in the bulbus venosus, external jugular veins, and in the liver. It is not uncommon to find a large pulsating liver in tricuspid insufficiency and no centrifugal, systolic wave in the external jugular vein. The presence or absence of the venous pulse will depend entirely in such cases on the closure or leakage of the valve in the vein above the bulbus venosus. The absence of swelling of the liver and hepatic pulse under similar conditions does not admit of such a simple explanation. There are no intervening valves in this instance; the swelling of the liver and its pulsation partly depend on the resistance of Glisson's capsule and the venous vasomotor resistance in the hepatic circulation.

Stasis in failing circulation is not always a matter of gravity and proximity of the lesion. Vasomotor influences also contribute, in many instances, to the site of massing of the blood. If massing of the blood in cardiovascular diseases were always an expression of hydraulic distress independently of physiological agents the problem would be much simpler. Regional stasis and regional œdema are occasionally encountered. A common experience in myocardial disease is to find an enlarged liver the sole sign of accumulation of blood on the proximal side of the left heart; at other times the signs may be purely renal and, in some instances, the signs may be wholly in the trunk or in the lower extremities. One instance particularly well illustrates this apparent inconsistency. The patient, a man aged forty years, had a septic endocarditis at the aortic orifice which terminated fatally in nine weeks. The lesion at the aortic orifice caused such marked stenosis of the orifice that it would just admit an ordinary lead pencil. There was no insufficiency of the aortic valves. Clinically and pathologically the patient presented the appearances of pure aortic stenosis without insufficiency. During the illness the pulse rate was never above 50 and during the rigors, which occurred every few days, the pulse was as low as 36, when the temperature was 106°. It was a pure bradycardia. There were no signs of extrasystole or heart-block. The pulse was of course very small, monocrotic, and of the tardus type on the anacrotic side. There was nothing to suggest any great vasomotor changes in the aortic distribution. Dyspnœa was not severe; cyanosis was slight. There was little clinical or pathological evidence of stasis in the pulmonary circulation. The left ventricle was not at all dilated or hypertrophied, and the right ventricle and auricle were very little dilated. The liver

was enlarged, extending three inches below the costal border. There were more evidences of an accumulation of blood in the splanchnic distribution than in the lungs. The situation in this case corresponds very closely to Elie Cyon's[1] conception of the function of the cardiac depressor. According to Cyon, irritation of the depressor nerve would account for bradycardia, weak impulse of the heart, and splanchnic hyperemia.

Such an instance is a rare exception to the purely hydraulic sequence of events usually seen in valvular and myocardial disease, but instances very commonly occur in which signs of local massing of the blood occur when the ordinary signs of sequential hydraulic stasis on the proximal side of the lesion are not demonstrable.

In the early so-called erethistic stage of cardiovascular disease we commonly find the patient complaining of cough from pulmonary hypermia when we cannot demonstrate a high tension in the pulmonary artery secondary to passive dilatation from a dilated left ventricle. In other instances the liver may be the seat of discomfort and sensitive to pressure, when there is not dilated right heart or a tricuspid insufficiency. Albuminuria from disturbance of the renal circulation may be present when the usual sequence of stasis from dilatation of the right heart is not demonstrable. All of these signs will sometimes disappear by employing some drug to lower the vasomotor resistance and the improvement will not be accompanied by any perceptible change in the size of the right or left side of the heart.

Another example of distribution of the blood in cardiac disease not in accord with pure hydraulic sequence is pericarditis with effusion. We would expect stasis in the venous system on the proximal side of the right auricle, as in myocardial or valvular disease, but such is not the case. In pericarditis with effusion there cannot be hyperemia of the lungs, because pericardial pressure retards diastole of the right as well as the left heart. So far as the systemic circulation is concerned the distribution of blood should be the same as in a weakened and dilated heart from mitral disease, viz., low aortic pressure and dilated veins.

The veins are greatly distended in such a case, but unlike the picture of stasis from myocardial insufficiency, in place of livid and cyanotic lips the face and lips are strikingly pale. Given a case of pericarditis with effusion and failing circulation, when the question of paracentesis arises, we can be safely guarded in our judgment by this single variation from the rule of blood distribution in failing circulation. If the patient's lips have grown pale with the progress of stasis, then withdrawal of the pericardial effusion is imperative. If his lips are livid and cyanotic we can be assured the obstruction is due purely to myocardial insufficiency and removing the pericardial fluid will not give relief. Just what vasomotor process is at work under these conditions is unknown, but the picture of stasis from pericardial tension strikingly differs from that in stasis from myocardial and valvular lesions.

The Heart's Impulse.—Under this heading we have to consider the excursion in systole and also in diastole. Modifications of the diastolic

[1] *Les nerfs du cœur*, Paris, 1905.

excursion may give very accurate diagnostic and prognostic information. There is no phase of cardiac diseases which is so variable and so inconstant in its significance as the cardiac excursion. A well-trained touch and sight are the only reliable means of observation in this field. The cardiogram is wholly unreliable when interpreted without control of sight and touch. The precordial impulse varies with the site of the cardiac region from which the tracing is taken. V. Frey[1] shows how widely the tracings vary when taken from different points on the exposed heart. The left ventricle near the lower portion of its left border, the right ventricle and right conus arteriosus (the sources of the precordial activity we ordinarily see and palpate) give very different tracings. So do the impressions gained by inspection and palpation over these areas vary in clinical practice. The negative and positive venous pulses and the carotid pulse are the only guides for determining the chronicity of phases of cardiac excursion. The accuracy with which these cardiac phenomena can be observed depends on the proximity of the heart to the anterior thoracic wall, which is determined by the size of the heart, the anteroposterior diameter of the thorax, and the volume of the lung.

When the heart is close to the anterior chest wall, as in adolescence, we can detect the downward and inward excursion of the apex during inspiration as clearly as portrayed by Röntgen rays. When the left and right ventricles are both dilated we can with relative accuracy define between the left and right ventricles and, in many instances of gallop rhythm, we can determine by palpation, as accurately as by auscultation, whether this comes from the right or left ventricle, and by comparing any phase of a precordial excursion with the pulses in the carotid artery and jugular vein we can determine whether an impulse is in the diastolic, presystolic, or systolic phase.

The old physiologists described the diastole as an active excursion of the heart's walls which forcibly opened the hand holding it within its grasp. Laennec described all impulses over the heart as systolic in time. To Bouilland (in 1835) the cardiac impulse was more than a mere systolic excursion. He recognized the share of diastole in cardiac impulses in chronic nephritis. Stefani,[2] a pupil of Luciani, has given very convincing experimental proofs of an active diastole; so there is no longer any question about the mechanically active diastole. Whether or not this active diastole is due to contraction of muscles antagonistic to the systole is not proved. Stefani enclosed the heart of a dog in a cup which was closed at the base of the heart with the reflected pericardium. The cavity of this vessel was connected by a T-tube with a manometer and pressure bottle, and the pressure in the cava, carotid artery, and cardiac receptacle simultaneously recorded. He found that the heart was able to deliver a wave in the aorta when the pericardial pressure was 25 cm. H_2O higher than in the cava, *i.e.*, within the right ventricle. Furthermore, when the pressure in the aorta was reduced to a minimum by restraint to the diastole from pericardial pressure, if the peripheral end

[1] *Die Untersuchung des Pulses*, Berlin, 1892, p. 109.
[2] Luciani, *Physiologie des Menschen*, 1905, vol. i.

of the cut vagus was irritated, the pressure in the aorta rose. If the vagus was cut the aortic pressure sank. The deduction from this experiment was that if nerve irritation is able to increase the force of the diastole, muscular activity must be the agent to produce it. Whether we have a muscular diastole in an antagonistic sense or not is not clear, but the diastolic precordial impulse is a physiological as well as clinical fact.

There are two points in the so-called long pause in which an impulse from the heart may occur, the diastolic phase in which the active diastole occurs and the presystolic period during which the auricle contracts. The former has the same chronicity as the diastolic murmur of mitral stenosis and the latter is synchronous with the presystolic murmur of mitral stenosis. Diastolic impulses of the heart have the same time relation to the systole as diastolic murmurs. The impulse may go over into the systolic impulse, thus giving the impression of a prolonged systolic impulse, or the diastolic impulse may be distinctly differentiated from the systolic impulse by a palpable and visible relaxation. The best examples of the latter are seen in cases of chronic interstitial nephritis and arterial sclerosis with high arterial pressure. This phenomenon is known as the *double impulse*. Very good examples of the less differentiated forms of diastolic-systolic impulse are seen in mitral stenosis and in myocarditis at the conclusion of acute infectious diseases, *e.g.*, influenza. The diastolic impulse of arteriosclerosis is a compensatory measure and a warning that the dilatation of stasis is impending. Palpable and visible gallop rhythm in mitral stenosis is accompanied by other signs which are equally or more significant. In myocarditis, or toxic conditions, following infectious diseases, the palpable gallop (which is also audible) may be the only sign of myocardial impairment, but it indicates the necessity of rest until the heart muscle has fully recovered.

In synechia cordis there is a diastolic impulse which, however, has not the same active character as seen in the impending myocardial insufficiency of arterial sclerosis. The writer has seen only four instances of this phenomenon and in these the diastolic impulse alternated with a strong systolic retraction over the apex. Although the precordial forward excursion was sharply synchronous with a venous collapse, the precordial excursion was more like a slapping impact than the heaving excursion of the diastolic impulse of chronic nephritis. It seemed very plausible in these instances of synechia cordis that the diastolic impulse was a direct elastic rebound of the thoracic wall resulting from systolic retraction. The phenomenon persisted over so long a period in various stages of compensation and insufficiency that it does not seem possible that the diastolic impulse could have been due to active diastole of the ventricle.

Lenhartz[1] suggested that the active diastole is responsible for hypertrophy of the left ventricle in cases of uncomplicated mitral stenosis. Only in diastole can there be any increased demand on the left ventricle in pure mitral stenosis, and there is sufficient clinical and laboratory evidence of the active diastole, as well as evidence of the diastole being directed by vagus function. Furthermore, there is good evidence of the

[1] *Münch. med. Wochenschrift*, 1890, Nr. 22.

diastole being associated with anabolic processes, and therefore a basis for hypertrophy of the left ventricle. When one considers the cardiac diastole as an active and essential function in the circulation, we realize how essential it is to carefully look for some manifestation of it.

The diastolic share in a presystolic impulse may often be very misleading to an examiner. The presystolic impulse over the apex in myocardial affections may often be mistaken for a prolonged and systolic impulse when in reality it is the sum of a presystolic and systolic impulse which is palpated. This very often occurs in myocarditis and mitral stenosis in which presystolic impulses are common. The diastolic impulse which is common in aortic insufficiency and chronic nephritis can be easily recognized both by inspection and palpation. To the practised touch all these modifications of the impulse are more apparent than a cardiogram will reveal. The prolonged impulse, the presystolic-systolic impulse, and the diastolic-systolic impulse can be recognized by palpation alone. It is a misfortune for the physician to believe these refinements of diagnosis can be elicited only by the so-called instruments of precision. There is far greater danger of being misled by the apparatus than by the senses. By this statement the writer does not wish to minimize the value of comparative tracings, but for the observations above mentioned all instruments of precision can be dispensed with.

Rôle of the Auricles.—We have seen there are two compensatory resources of the ventricles in maintaining the mass movement of the blood, viz., increased force of the systole and hyperdiastole. Do the auricles assist in these compensatory efforts? By the time a patient with chronic endocarditis (mitral stenosis, for instance) comes to autopsy we find a thin-walled and greatly dilated left auricle. At autopsy the observation usually stops with this information. To determine whether there may be an hypertrophy of the auricle requires the adoption of a method of separating all the chambers and weighing them apart from one another.

That the auricle does hypertrophy has been found clearly enough in patients with old mitral stenosis who have met with sudden death from other causes. The wall of the left auricle in such cases has been found as thick as the wall of the right ventricle. Such a demonstration requires the heart to come to anatomical examination while a fair state of compensation persists. There are other pathological findings which indicate dispensableness of the auricle. In veterinary literature there are a number of instances described in the horse in which the right auricle has undergone complete calcification. The endocardium was intact, but the auricular wall was as hard and rigid as the shell of an ostrich egg. During life there were no signs of circulatory disturbances. There are, however, other instances of calcification of the myocardium of both ventricles where the mural structure at the atrioventricular sulcus was transformed into a rigid ring. The ventricular myocardium showed such extensive deposits of lime salts that section with a knife was very difficult and the papillary muscles were so involved that they projected into the ventricular cavity like rigid stalactites. From the descriptions, one is forced to believe the circulation was largely maintained by the auricles.

That the auricle is capable of throwing a wave of blood into the aorta

is well demonstrated in the studies of pulsus bisferiens. D. Gerhardt found the first elevation of the carotid in a case of double pulsation of the artery to be synchronous with systole of the auricle. The writer has observed the same in a case of pulsus bisferiens. Hürthle has succeeded experimentally in demonstrating an auricular wave in the aorta. He did not produce a pulsus bisferiens in his animal, but showed the auricle could develop a pressure equal to 20 mm. Hg. If, by irritation of the vagus, the aortic pressure was reduced to 12 mm. Hg. there was then a slight elevation in the aorta which preceded the systole of the ventricle and was synchronous with the auricular systole. Such observations compel us to give some heed to the auricle as a motor organ.

It is a common experience in combined mitral stenosis and insufficiency to find only a presystolic murmur and thrill with a loud tympanitic systolic tone over the apex. There is no suggestion of mitral leakage, although insufficiency is as clearly present anatomically as the stenosis. When compensation is disturbed in such a case we have quite another picture. As signs of stasis develop in the pulmonary vessels, acute dilatation of the heart and arhythmia, the presystolic murmur and thrill disappear. We have instead a gallop rhythm over the apex of the left ventricle, and the systolic sound is either accompanied or obscured by a loud blowing murmur. The presystolic elevation and sound over the apex may be due to the hyperdiastole of the ventricle or to the wave from the dilated left auricle. As the dilatation of the heart and pulmonary stasis disappear we have restoration of the former conditions. Instead of the presystolic elevation and sound over the apex of the heart we again have a palpable presystolic thrill and a presystolic murmur; the systolic murmur disappears and we again have during the ventricular systole a loud, sharply defined, systolic sound. Samways attributes this series of events to the rôle of the auricle, and explains it in the following manner: The total pressure on the bounding walls of a hollow sphere increases directly as the square of the radii. The resistance of the walls of a hollow, elastic sphere, with a certain wall thickness, will be inversely as the square of the radius. Thus, the auricle in its contracted systolic phase has an obvious advantage over the dilated ventricle. Now, if we can conceive the systole of the auricle to be maintained longer than the usual time, the auricle would successfully guard the mitral orifice against regurgitation during the systole of the dilated ventricle. For, in the dilated state the contraction of the ventricle is much less complete than during compensation. Consequently, the ventricle remains at a physical disadvantage in its contention against the guard of the auricle. Such an explanation requires a great prolongation of the auricular systole. The systole of the auricle is estimated to occupy only one-third as much time as that of the ventricle; so if the auricle were to guard successfully the mitral orifice during the entire ventricular systole, it must prolong the time of systole four times that of the normal period. Such a conception is inconsistent with the slight variation of systolic time of the ventricle under widely differing conditions.

Although this conception is repugnant to the purely physiological conception of the spacing of the cardiac cycle, it seems very possible that some

such function on the part of the auricle must guard the so-called buttonhole mitral orifice in the expulsion phase of the ventricular systole. Potain ascribes the presystolic elevation of the ventricle in gallop rhythm to the systole of the auricle, and possibly correctly, for it remains to be clearly shown whether this presystolic elevation is due to hyperdiastole on the part of the ventricle or to the passive distension of the relaxed ventricular wall by a wave of blood from the auricle. These considerations make it apparent that the auricle merits some serious consideration as a motor organ and may play a considerable compensatory part in the distribution of blood under pathological conditions.

Valvular Mechanism.—The wonderful elasticity and resourcefulness of the myocardium in adapting itself to varying demands has always elicited the admiration of students of physiology. Although not so obscure in their methods and structure, the perfect function of the valves is not less marvellous.

The tricuspid and mitral valves are closed the instant the pressure within the auricle becomes less than the pressure in the ventricle, and that occurs independently of the ventricular systole. Experiment has shown that the flow of blood from the auricle into the ventricle forms eddies and currents between the wall of the ventricle and the cusps of the valves; so that there is a force at work in the current of the entering blood which tends to approximate the edges of the valves and is prevented from doing so by the pressure from the auricle. Directly the auricle ceases its contraction there is a force within the ventricle which (no longer hindered by the pressure from the auricle) seals the atrioventricular orifice. If this were not so, then there must always be a slight regurgitation attending every systole of the heart. The tricuspid and mitral valves are closed before the systole of the ventricles begins. In this manner the auricle shares in the production of the systolic sound. The ventricles now have a point of opposition for the expulsion of the blood into the aorta and pulmonary artery, respectively. There is an appreciable lapse of time between the commencement of systole and opening of the semilunar valves. This mechanism of the auricular wave closing the atrioventricular valves is probably responsible for the sound heard over the ventricle in cases of heart-block when the auricular contraction is not followed by a ventricular systole. There is a similar provision for the closure of the semilumar valves.

Ceradini used the following demonstration to show how the currents in the aorta contribute to the closure of the semilunar valves: A vertical glass tube is equipped with a piston at the bottom and the tube filled with water containing visible substances in suspension, so that the direction of currents may be detected. The piston is pushed upward and with its upward progress the particles suspended in the column of fluid are seen to attain varying velocities. There is a central axial stream in which the speed is nearly double that of the average speed of the particles in suspension. The particles near the periphery of the tube cavity progress very slowly and are overtaken by the piston in its upward progress. These are swept into the axial stream by a centripetal current from the periphery; they are seen to fly before the piston in the axial stream and on reaching

the top of the liquid are again carried toward the periphery by centrifugal currents. If the piston is stopped the column of fluid is seen to be divided into two parts. The central axial stream continues forward and the tardy peripheral stream reverts toward the piston. At the surface of the fluid a centrifugal eddy is seen, and at the piston a centripetal eddy, in which the visible particles are seen rushing from the periphery toward the central axial stream. This reverting eddy is believed to be the factor which closes the valves the instant the intraventricular pressure is less than that within the artery.

The attempts to mark with absolute accuracy on a cardiogram just when the closure and opening of these two sets of valves occur have not met with uniform results among various observers. One reason is probably the want of any perfect model of a cardiographic tracing. The tracing of the exterior of the heart is a combination of the contraction curve of the heart muscle and the ventricular volume. This may vary widely and the diastolic impulse modify the excursion of the heart muscle; so also may the closure of the ventricular valves clinically occupy varying points on the precordial excursion. This will depend entirely on the character of the ventricular diastole, and how much of a precordial excursion is caused by the active diastole and how much of a precordial impulse is imparted to the ventricle from the systole of the auricle. So the presphygmic and "prosphygmic" rise of the precordial region are phenomena which will change with the demands and efficiency of the heart muscle. They are not constant factors under pathological conditions. It is an error to assume that the instant the palpable impulse of the heart begins the atrioventricular valves are closed and the semilunar valves are opened.

The active diastole of the ventricle, the passive distension of the ventricle by the current of blood from the auricle, and the closure of the atrioventricular valves before the beginning of the ventricular systole may all enter into the palpable precordial impulse. Failure to consider these factors will lead to misconceptions of the character of systole. A so-called prolonged systolic impulse over the heart may be partly presystolic. By observing the waves in the jugular veins and comparing their chronicity with that of the carotid pulse and the duration of the precordial impulse, the examiner can arrive at just as accurate conclusions for diagnostic purposes as by the use of instruments. So far as the practical diagnostic data are concerned in this relation, thoughtful inspection and palpation are the only means requisite for the diagnostician.

The time of closure of the semilunar valves is of course the instant the pressure within the ventricle is less than that in the aorta. The possible lapse of time between the closure of the aortic valves and the diastolic sound or impact is not appreciable and cannot be the source of any misconception of the cardiac cycle. The diastolic sound or the diastolic impact over the base of the heart or the aorta or pulmonary artery is taken as the point of closure of the semilunar valves.

Myogenic and Neurogenic Theories.—Investigation of myocardial diseases has, in recent years, given a new significance to the question of cardiac autonomy. How and where does the automatic stimulus of the heart originate? How do the nerves share in the cardiac activity? How

is the coördination between the chambers accomplished? All these problems are resolved into the question: Is the autonomy of the heart myogenic or neurogenic in origin? Although the problem is unsolved there has been much of interest produced by champions of both sides of the question which has contributed to our knowledge of the myocardium and its nerve supply. These studies are the basis of modern views on cardiac arhythmia (Engleman and Wenckebach).

The myogenic theory has gained much favor:

1. There are pathological reasons for this view. Lesions of the heart muscle and skeletal muscles have little in common and lesions of the myocardium have a much closer analogy with diseases of glandular organs, viz., the kidney and liver. The myocardium is now regarded as a homogeneous blending of discrete structural cells. It consists of numberless branched chains of singly nucleated membraneless cells, between whose contractile substance the most intimate contact exists. There is supposed continuity of substance between the contents of several cells. This conception of the heart muscle is quite different from our idea of skeletal muscles.

2. Heart beat has never been produced by stimulation of any nerves supplying the heart.

3. Both vagi have been cut, and, after degeneration of the nerves had set in so that stimulation of the peripheral ends no longer affected the heart's rhythm or rate, the Stanius ligatures were applied, with the same results as when the vagi were intact.

4. The dog's heart has had all its nerve connections severed from the brain, spinal cord, and sympathetic system, and survived eleven months.

5. Transmission of contraction waves in the myocardium has been shown to be independent of the continuity of nerve structures in the heart muscle by making a series of zig-zag incisions through the wall of the turtle's heart parallel to the base. These incisions are made so that there must be a solution of continuity of all nerve paths from the base to the apex. Only muscular continuity is left, and that of course remains only through very narrow connections. In spite of these sections the rhythmic contraction wave is not abolished.

6. Development of electricity and heat shows the myocardium to be the seat of very active physiological oxidation. Evidence has been added to show that cardiac autonomy is dependent on metabolic processes within the myocardium. Rhythmic contractions of auricles and ventricles have been restored in the human heart after postmortem removal of the heart from the body, by irritating the myocardium through the coronary vessels with a nutrient artificial serum impregnated with oxygen.[1]

7. Embryological evidence shows that the rhythm of the heart beat is established before cardiac ganglia (which are sympathetic in origin) have entered the heart. This evidence alone would be decisive if the negative could be absolutely proved, but the failure to demonstrate their presence does not prove their absence.

In spite of all this evidence contributing to the myogenic view,

[1] Kuliabko, *Pflüger's Arch. f. d. Gesamt. Phys.*, 1903, vol. xcvii; also Hering, *ibid.*, vol. xcix.

Kronecker[1] has shown that there is a centre in the dog's heart, located in the upper and anterior quarter of the interventricular septum, which, if pierced with a needle, will cause death. The trauma from such a procedure must be inflicted on a nerve centre, as otherwise so slight an injury to the heart wall could not cause death. Kronecker says the intracardiac ganglia produce the rhythmic contractions of the heart. "Even if the myocardium is capable of independent contractions under certain conditions, the muscle alone cannot do it. The myocardial ganglia receive and transmit stimuli from one chamber to another and thus maintain a rhythm and coördination between the several chambers which would be impossible if there were merely myocardial autonomy."

The neurogenic theory regards the ganglia of Remak at the junction of the vein with the auricle as the origin of automatic stimuli. These stimuli are transmitted along the network of nerves from auricle to ventricle. The halt between the systole of the auricle and the ventricle is conceived to be caused by the intervention of the ganglia of Biedert.

Uexküll[2] has presented biological evidences, from the study of simple forms of sea animals, which tend to harmonize the two views of automatic rhythm. He has shown the interdependence between muscle and nerve centre in automatic rhythm, the refractory period, and "all or nothing" law of contraction which is observed in the myocardium.

The champions of myogenic autonomy have given us an analysis of the basic factors of myocardial activity and have assigned their direction to the nerve supply. These factors are automatic production of stimuli, response to stimuli, transmission of stimuli within the heart, and contractility. According to Engleman[3] each factor can be modified in a positive and negative sense.

Those influences which affect the periodic contraction stimuli, *i.e.*, the heart rate, are known as chronotropic influences. Those controlling the contractile responsiveness of the myocardium to stimuli, *i.e*, those which determine the minimum stimulus to which the heart will respond, are known as bathmotropic influences. Those affecting the transmission waves in the heart are known as dromotropic influences. Those modifying the strength, size, and duration of the contraction are known as inotropic influences.

Arhythmia.—Investigations of cardiac autonomy have led to new conceptions of cardiac arhythmia. The basis of these studies is an analysis of pulsus bigeminus—which is regarded as an allorhythmia or pararhythmia due to extrasystole. Primary to the idea of extrasystole are several characteristics of myocardial response to stimuli which have been recognized for many years, viz., (*a*) "the all or nothing law of contraction;" (*b*) failure of the heart muscle to respond to stimuli during a certain part of the cardiac cycle known as the refractory period, and (*c*) the compensatory pause.

(*a*) Although vigor of response of skeletal muscle to nerve stimulus does not sustain a constant proportion to the vigor of the stimulus, still there is

[1] *Zeitschrift f. Biol.*, 1897, vol. xxxiv.
[2] *Ergebnisse der Physiologie*, vol. iii, Abth. ii.
[3] *Pflüger's Archiv* from 1895 to 1897

some constancy in the degree of contraction of skeletal muscles after varying magnitudes of stimulation. In the heart muscle this is not the case; no matter how strong the stimulus may be, if the heart responds at all it responds with all its strength. This is known as "the all or nothing law."

(*b*) During a ventricular systole the heart will not respond to any stimulus with an added contraction, however strong the stimulus may be. After the completion of the systole, irritability and contractility of the muscle gradually return until the normal period for the following systole occurs. The period in which the heart will not respond to any stimulus is known as the refractory period. In the succeeding period of available contractions, the earlier in the diastole a stimulus is applied the stronger it must be to elicit a response. As we approach the point in the diastolic phase for the following systole a lesser stimulus is required to produce a contraction. The occurrence of contractions in this period of relative refractoriness is known as the phenomenon of extrasystole.

(*c*) If the heart is now permitted to follow its automatic rhythm after the production of an extrasystole, it will be found that the pause following an extrasystole is longer than in the normal automatic rhythm; if sufficiently long to make the distance between the first and third contractions the same, a systole of the normal rhythm could have occurred instead of the interpolated extrasystole. This lengthening of the diastolic time after an extrasystole is known as the compensatory pause.

Genuine arhythmia occurs when there is a disturbance in the origin of automatic rhythm, viz., at the junction of the veins with the auricles. Genuine arhythmia is characterized by the absence of compensatory pause in the arterial pulse and the absence of signs of heart-block in the jugular veins. The pulse volume accompanying an extrasystole will be smaller than a normal pulse on account of the shortened diastole, rendering the filling of the ventricle incomplete.

Hypertrophy and Dilatation of the Heart.—The terms hypertrophy, accommodation, adaptivity, and compensation have been sources of a large controversial literature in medicine. As in most medical polemics, the kernel of controversy has been the use of terms rather than facts and clinical experience. One phase of the controversy has been the questioning whether a heart which has responded with hypertrophy to an increased demand on its work may enjoy the same amount of reserve energy as before. In other words, does the individual begin life with a certain number of foot pounds of energy on which he may survive a certain length of time, provided he draws on his reserve at a certain rate, or, should occasion demand it, may he increase his store of energy, meet an increased rate of demand, and still enjoy an available energy equal to his original endowment?

The heart is capable of performing very many times the sum of daily work which an ordinarily regulated life demands. This property it has in common with other organs. We know the kidney and liver may enjoy a genuine hypertrophy and not sacrifice the working value of any of the total structure. Can we secure the same result in the heart, or does hypertrophy always mean an encroachment on the available sum of energy?

Under one condition at least hypertrophy is a welcome sign. At birth the right and left ventricles have the same wall thickness. With the beginning of extra-uterine life there is an increased demand on the left ventricle. To maintain the systemic circulation now requires a greatly increased expenditure of energy and the left ventricle responds to this demand with hypertrophy.

This physiological hypertrophy must also be accompanied or rather preceded by dilatation just as dilatation primarily accompanies the hypertrophic process from plethora or physical exercise. With the transition from intra-uterine to extra-uterine life, the enormous increase in metabolism in all the body structures requires a volume of the cardiac cycle greatly in excess of the prenatal demand. To meet this sudden demand the heart must dilate and subsequently undergo hypertrophy. This is a benign hypertrophy and as welcome as hypertrophied skeletal muscles to the athlete. By graduated exercises the athlete may increase the efficiency of his heart muscle as well as his skeletal muscles. In this connection it must be remembered that the athlete's myocardium is subjected only to periods of excessive work and merely the ordinary demands of life in many hours of waking and sleeping. The heart which is hypertrophied as a consequence of permanent changes in the cardiovascular system never has freedom from the increased labor. We sometimes meet with examples of pronounced impairmant of the heart valves in a patient who has been wholly unaware of any discomfort which could be attributed to a defect in the circulation. These persons are capable of performing feats of strength and skill which would overtax many hearts we consider normal. There is no method of estimating the reserve energy in prospect for such an individual, nor is there any method of learning what his heart might have equalled without the valvular lesion. Sometimes we meet with great surprises in the exhibitions of reserve energy of a crippled heart.

Transition from a state of compensation to incompetence seems often very sudden. A patient is brought to the hospital with a greatly dilated and rapid heart, pulmonary œdema, hepatic stasis, and œdema of the legs. From the history we learn that this patient never experienced any symptoms which could have been due to an impaired circulation until a few hours before, when suddenly he experienced a sudden pain in the precordial region, attended with dyspnœa and great exhaustion. Insufficiency of the myocardium which develops suddenly is due to the vicious cycle created by lowering the pressure in the coronary arteries, which occurs directly the ventricle is unable to maintain the required aortic pressure. Thus, at the very time when the heart muscle requires the greatest supply of nutrition, the supply of blood lessens.

Sometimes death occurs very suddenly without the slightest premonition of incompetence, as in cases of fatty degeneration of the muscular cells and myocarditis following acute infectious diseases, *e.g.*, diphtheria, typhoid fever, and pneumonia. In other cases the myocarditis following infection may be indicated by very great dilatation of the heart, which recedes as the myocardium improves and the patient goes on to a good recovery. Why one case is attended with all the classical signs of myocardial insufficiency and terminates in recovery and the other ends in

sudden death without the slightest dilatation as a warning remains a mystery. There is, too, great inconsistency between pathological findings and the clinical course of myocardial diseases. We must be content in our diagnosis of such cases to recognize the functional defects rather than the exact anatomical findings.

Many times the functional impairment will manifest itself long before anatomical changes occur and often great anatomical changes will occur before the slightest functional disturbance appears. Very extensive malignant disease of the heart muscle may be found without having given the least sign of functional disturbance as a part of the clinical course of the disease. Even in experimental myocardial disease there is not the loss of reserve energy we would expect. A dog is poisoned with phosphorus, which results in extensive fatty degeneration of the myocardium. If now the aorta be compressed, the heart will maintain a flow of blood against a pressure two or three times greater than the normal aortic pressure of the dog. The ability to maintain a pressure of 200 mm. Hg. against resistance must not be interpreted, however, as being equal to maintaining 200 mm. Hg. pressure as a result of physical exercise. The former instance is one of pure external resistance unattended with the great mass movement of blood in the aortic and pulmonary circulation and the greatly increased metabolic processes which occur in physical exercise. Thus, we see patients with arterial sclerosis maintaining an aortic pressure of 300 mm. Hg., or the pressure may change from 220 mm. Hg. to nearly 300 mm. Hg. without causing any discomfort. But the patient is not able to perform the slightest physical exercise without great discomfort.

A normal blood pressure does not imply normal blood movement; this is often a source of confusion. There is an apparent inconsistency between an arterial blood pressure nearly normal and pulmonary and hepatic stasis. This inconsistency is apparent, not real. Vascular contraction compensates for diminished filling of the vessel. Mitral stenosis offers very good examples of this condition.

Thus far we have had under discussion the compensatory or accommodative property of the heart in its systolic phase, but the diastolic phase probably plays as great a rôle. It is possible that some instances of death in myocardial disease are due to loss of its diastolic property. The diastole is not so easily studied as the systole, and our knowledge of the manner in which diastole is accomplished is so vague that the physiological knowledge cannot be applied to any known pathological changes in the myocardium.

We have seen how diastole enters into the compensatory measures of the heart in the beginning of extra-uterine life and in physical exercise. The same diastolic aid must be invoked in the compensatory procedures of aortic insufficiency, the plethora of gluttony, and in emotional excitation of the heart. If this dilatation gives the incentive to trophic changes in the myocardium, then an eccentric hypertrophy appears; the capacity of the chamber is increased and the ventricle can deliver a greater volume of blood under an increase of the total intraventricular pressure, with a smaller volumetric excursion of the cardiac wall. There may be changes in the circulation which demand an increase of the systolic effort without

increased demands on the diastolic function, *e.g.*, increased vasomotor resistance. There follows then a hypertrophy of the wall without dilatation which is known as concentric hypertrophy. Later, when a concentric or eccentric hypertrophy of either ventricle is no longer able to maintain the resistance against which it is working, we have a passive dilatation with loss of tone of the heart muscle. This is known as the dilatation of stasis and is always accompanied by incompetency, while the active compensatory dilatation may be sufficient to increase sixfold the volume of blood (delivered by the systole of the ventricle) and compensation remains undisturbed.

In acute dilatation of the heart with stasis, which results from excessive exercise, there is lacking the trophic stimulus which, under favorable conditions, leads to hypertrophy. Whether or not this sequence of events occurs in a heart which is perfectly sound up to the time of dilatation is a question. It is possible that such hearts have experienced some lesion prior to the event which attended the dilatation. Such cases have been observed, but there are many other instances recorded in which the heart was functionally sound up to the time of the acute passive dilatation.

Dilatation and hypertrophy of the heart most commonly result from malformation or disease of the myocardium, the valves or pulmonary vessels, either primary or secondary to lung affections, or diseases of the aortic system. Purely psychical and nervous excitement may give rise to all the signs, viz., cardiac enlargement, arhythmia, and murmurs. The painful emotions especially, which are the more intense and lasting, bring in their train a series of objective and subjective symptoms which betray myocardial impairment. Grief or loss of fortune is sometimes the direct cause of these symptoms as well as prolonged anxiety and fear of death. Prolonged and uncontrollable laughter in a young healthy girl has been observed to be followed by acute dilatation and asystole. Excessive venery, gluttony in eating, and drinking of malt liquors are commonly recognized as direct causes of myocardial impairment. Frequent and prolonged efforts at coughing in acute and chronic diseases of the respiratory tract, when there is not sufficient involvement of the pulmonary vessels to be a contributing factor, are also an exciting cause for myocardial disease.

Toxic influence, as in nephritis and Basedow's disease, may cause both hypertrophy and dilatation of the heart. The writer saw one instance of clearly demonstrable hypertrophy and dilatation of the left ventricle with high arterial pressure in a woman who, for many years, drank regularly as much as ten cups of coffee a day. All these signs diminished in a few months after discontinuing the use of coffee.

In estimating the causative factors of any myocardial affection it is often just as important to learn the habits of life and social influences which surround a patient as to learn the history of preceding diseases.

The Work of the Heart.—Physiological experiment has shown the energy developed by the left ventricle to expel 60 cc. of blood against an intra-aortic pressure of 150 mm. of Hg. is 122.4 gram-meters. The work necessary to give this volume of blood under such pressure a velocity of 0.5 meter a second is 0.72 gram-meter. It is apparent from this estimate

that a very small part of the total energy expended is employed in giving the volume of blood its velocity. The great mass of work is represented by the pressure against which the ventricle is contracting. Such estimates, however, do not admit of direct incorporation of the clinical valuation of work performed by a heart, nor do they give us any prognostic information. Diseases of the cardiovascular system mean much more than a mere problem in hydraulics: the problem of hydraulics is intimately and intricately linked with physiological problems, both vital and chemical, which take place in the muscles, glandular structures, lungs, central nervous system, and in the heart itself. We find the relation between the heart rate, blood pressure, and size of the heart maintains a very inconstant relation to the resources of the patient. We are often disappointed to find the patient derives little benefit from changes in the blood pressure which would seem to greatly improve the mass movement of the blood. Our limitations in clinical studies of the mass movement of the blood are the study of the blood pressure and duration of the pulse. The arterial pulse, which is an expression of the heart's work against peripheral resistance in a closed system of elastic tubes; is the only tangible phenomenon from which we can form an idea of the efficiency of blood hydraulics.

A very important factor, always to be investigated, is the elasticity of the aorta and its branches. The pulse in the smaller arteries is an expression of two pulses, the ventricular and the aortic pulses. That portion of the pulse which outlasts the ventricular systole is manifestly due to the elastic property of the aorta. The total energy must have its origin in the heart itself, but the aorta contributes much to the economy of that expended energy. The energy expended in stretching the aorta is stored up as potential energy, to be released as kinetic energy after the closure of the aortic valves.

The value of an elastic tube intervening between a source of liquid stream and its outflow at a terminal orifice of small caliber can be illustrated by the following experiment: An elastic outflow tube *A* is fitted to a pressure bottle. The tube *A* terminates in two branches, one a flexible rubber tube, the other a rigid glass tube. Both branches terminate in equal orifices, which have a caliber much smaller than the channels of the two branches. When the flow is continuous an equal amount of fluid escapes from the two orifices within a given time. If the stream be interrupted by rhythmic compressions at the rate of one a second, the volume of fluid which escapes from the flexible branch in a given time will be about double the amount which escapes from the rigid branch. The pressure of the head is the same in both instances; but the flexible branch gains much in time if the resistance of the orifice is sufficient to cause distension of the flexible tube.

The elasticity of the aorta accomplishes the same result for peripheral circulation by maintaining a constant flow when the original source of pressure (the ventricle) is interrupted. Although the aorta does not contribute any energy for propelling the blood, it does by virtue of its elasticity increase the pumping efficiency of the ventricle. Elasticity of the aorta affords advantage in time, in expenditure of energy analogous to

the advantage of distance in the expenditure of power in a lever of the first class. If the elasticity of the aorta is lost, then we approach a condition in which the total mass movement of blood must be accomplished during the time of ventricular systole. Propulsion of blood toward the periphery during ventricular diastole is largely sacrificed. Therefore, the same mass movement of blood in a much shorter time will require a greater maximum pressure than under normal conditions when the elastic aorta contributes during cardiac diastole the potential energy stored during a cardiac systole.

From these considerations it is quite clear how the hydraulics of the circulation in chronic aortitis are identical with those of insufficiency of the aortic valves, viz., a great and sudden excursion of the artery during systole and a katacrotus of short duration, a capillary pulse and loud pistol-shot tone in the femoral artery, and hypertrophy of the left ventricle. If resistance to the peripheral flow be diminished by depressor motor influences, then there will be a pulse of short duration, a capillary pulse, and loud pistol-shot tone in the femoral artery. In one case of this character the pistol-shot tone in the femoral artery was so loud that it was distinctly audible at a distance of six feet from the patient; this sign disappeared after the administration of adrenalin.

Flow of blood in the artery may have the same character in widely differing conditions, viz., insufficiency of the aortic valves, aortitis, and depressor motor influences. Differentiation between these causes must be arrived at by study of other factors.

Duration of the pulse beyond the closure of the aortic valve is an expression of aortic elasticity contending against peripheral resistance and internal friction or the viscosity of the blood. The character of the katacrotus can be modified by the volume of the systolic wave from the ventricle, the elasticity of the aorta, the viscosity of the blood, and the vasomotor resistance.

Dicrotism is an expression of differentiation between the ventricular wave and the wave from aortic contraction. To accentuate dicrotism above the normal degree, the favorable conditions are diminished peripheral resistance and a shortened systole of the ventricle. The indispensable factors for dicrotism are an elastic aorta and a certain relaxed vasomotor tone. There must be sufficient vasomotor tone to compel distension of the aorta during the ventricular systole, and there must be sufficient elasticity of the aorta to store a considerable amount of blood during the heart's systole. Vasomotor paralysis causes the dicrotic wave to disappear. This is seen in the progress of meningitis, typhoid fever, and sepsis. Particularly in typhoid fever and sepsis is the transition from dicrotism to pulsus celer a marked feature with the progress toward vasomotor exhaustion.

Shortening of the cardiac systole will bring out dicrotism as seen in two conditions which differ very widely in other respects: the hyperdicrotism after prolonged muscular effort as described by Kraus, and the hyperdicrotism of paroxysmal tachycardia as exhibited in the case of a tabetic patient described by Pal. In hyperdicrotism after physical exercise we have another factor which contributes to the manifestations of dicrotism,

namely, arterial relaxation. It would be impossible to have dicrotism with a high arterial maximum pressure without arterial relaxation. In the latter the tonometer registered a maximum pressure of only 60 mm. Hg., whereas in the athlete the maximum pressure is increased directly after exercise. In both cases, however, there is sufficient shortening of the expulsive phase of ventricular systole to cause the ventricular and the aortic wave to alternately reach the distant arteries.

If the vasomotor resistance is greatly increased, then dicrotism is obscured by the heightened aortic and arterial tension and the oscillations of elasticity which give the picture of pulsus durans and prolonged katacrotus.

A prolonged katacrotus and high maximum pressure are not invariable accompaniments. Occasionally one meets with a greatly prolonged katacrotus in the brachial artery where the artery literally struggles to empty itself during the cardiac diastole, although the tonometer reveals a normal maximum pressure. In such cases we are not dealing with a widely spread increased peripheral resistance, for if the carotids and femoral arteries are examined we may find the katacrotus much shortened. The controlling factor, however, is resistance in the splanchnic distribution, and the pulse in this area is not accessible. It is thus clear how important is an examination of all the accessible arteries, and how misleading the pulse in a single artery may be.

The character of anacrotus and katacrotus are far more important than the maximum blood pressure in estimating the hydraulics of blood flow. There is no instrument of precision which suffices for this purpose. The sphygmogram, like the cardiogram, is only of service when controlled by trained observations of sight and touch. For purposes of graphic comparison it is useful, but it cannot be substituted for trained observation. Various modifications of the tonometer have proven to be of much greater service than the sphygmograph. Although the general use of the tonometer may be attended with a considerable margin of error, it nevertheless has enabled observers to communicate and record their observations with relative accuracy. Before the employment of this instrument there were no means of approximately recording and comparing our observations on blood pressure.

With blood pressure, however, the matter is very different. We are dealing with a single attribute which cannot be described in terms other than a standard of measurement. The trained touch can accurately recognize an increase or diminution of pressure in one of the larger arteries, such as the brachial, carotid, or femoral, but the tactile experience of an examiner is not communicable to others, nor can it be stored in the examiner's memory for comparative studies.

The tonometer, like other instruments of precision, has served to stimulate physicians to better tactile observations on the pulse. Peripheral resistance can be estimated only as expressed in the peripheral flow and the modifications of the anacrotus and katacrotus of the pulse.

In addition to the elasticity of the aorta and its branches and peripheral resistance from the capillaries and minute arteries the only factor of resistance to the arterial flow of blood is in its viscosity or internal friction.

Of all these factors the only one which can be estimated clinically with accuracy is the aortic resistance. As above mentioned, the bulk of the work of the left ventricle is expended on stretching the aorta and its branches. This element of the work can be measured with the tonometer. All the other factors which modify the flow of blood can be estimated only by the senses.

Dyspnœa.—Dyspnœa from disease of the cardiovascular system may be pulmonary, toxic, or nervous in origin. The causes of pulmonary dyspnœa are the slowing of the blood current in the lung, thus impairing the interchange of oxygen and carbon dioxide. Besides slowing of the blood current there is a secondary bronchitis consequent upon stasis and the disease in the alveolar epithelia and thickening of the blood capillary walls. All of these conditions contribute to the production of chronic dyspnœa. *Toxic* sources of dyspnœa in disease of the circulation are not chemically proved; we have nothing more than the direct association between increased renal elimination and the relief of dyspnœa. It is not an uncommon experience, in observing cases of arterial sclerosis, to see a marked disproportion between the degree of dyspnœa and the relative size of the left and right heart, pulmonary stasis, and massing of the blood. There may be no œdema, slight evidence of massing of the blood either in the pulmonary circulation or in the liver, and no albumin in the urine, and yet, after the administration of diuretics, such as caffeine and theobromine preparations, we find from the brisk diuresis there has been a decided retention of fluid within the body and apparently with some toxin, for directly diuresis is accomplished the dyspnœa is relieved. The disproportion between the physical evidences of retention in such a case and the dyspnœa is seen in other cases of valvular lesions: pronounced œdema in pendent parts, very considerable massing of blood in the liver, and very much less difficulty in breathing. The kidney is not the only organ which may be associated with the production of toxic dyspnœa, for with disturbance in venous and capillary pressure come changes in osmotic pressure and metabolism of the organs, so that the liver may be the source of an intoxication in two ways: one by the failure to protect the organism against toxins already formed and possibly by the production of toxins of its own. So far as clinical experience goes in these cases, we are justified in speaking only of the renal source of dyspnœa. With this, however, we do not mean there is always a lesion of the renal structure; nor is it perfectly clear that the work of the kidneys independently of structural disease is responsible for the condition. We are not justified in going farther than to state that experience teaches that when there is a disproportion between the physical manifestation of disturbed blood distribution and dyspnœa, we find the patients gain great relief by stimulating the kidney to increased activity.

The purely *nervous* source of dyspnœa is not so clear as either of the forms above described, yet there seems sufficient clinical evidence, moderately well supported by experiment, to show the reasonableness of this source of dyspnœa in cardiovascular disease. The nerve supply of the heart and lungs is not only anatomically closely linked, but there is a very close clinical relation between the two. It is sometimes very difficult to

differentiate between dyspnœa consequent upon subacute or chronic circulatory disturbance in the lung and dyspnœa due to a pure nervous reflex which is quite independent in its circulatory disturbance from the basic disease. The nervous relation between the heart and digestive tracts is more apparent in clinical experience. It is common to see vomiting, meteorism, and great subjective distress, referred to the stomach and even the bowel, associated with myocardial disease, particularly the acute disturbances which result from diseases of the coronary arteries. We know there is a trophic influence on the lung embodied in the functions of the vagus nerve, as evidenced by pulmonary œdema and acute emphysema due to disease of the nerve trunk and the vagus nuclei. Acute bronchial asthma with emphysema (both spasmodic in character) occur in diseases of the mediastinum, and acute pulmonary œdema is an occasional incident in the history of diseases involving the bulbar nuclei. There are two classes of *reflex* dyspnœa in cardiovascular disease. One is from the stomach and the other from the aorta and left ventricle. The act of digestion requires an increased supply of oxygen and an increased mass movement of the blood, and, in this way, may suffice to induce dyspnœa in a patient with an uncompensated cardiac lesion. In many patients with cardiovascular disease, particularly with those having diseases of the coronary arteries, dyspnœa is precipitated directly after taking very moderate amounts of food, and that, too, when there are no signs of stasis in the pulmonary or systemic circulation. It seems this dyspnœa must be the result of a diffuse reflex vagus stimulus to the heart and lung, for it is manifestly disproportionate to the reserve energy the heart exhibits in meeting demands of muscular exercise.

Diseases of the aorta are particularly liable to be accompanied by paroxysmal attacks of dyspnœa. These patients are commonly awakened in the early hours of the night, sometimes with precordial pain and other times with mere feeling of anxiety and distress in breathing. On examining such patients we are surprised to find very slight evidences of any change in the circulation from those we have been accustomed to see in the patient from day to day. Although the patient is extremely dyspnœic at ten o'clock at night, the same day he was comparatively comfortable so far as his cardiovascular disease was concerned. We are surprised and disappointed, in making a physical examination, to find the blood-pressure and volume of the artery little changed; and, although we regard the dyspnœa as cardiac in origin, there are not the usual evidences of stasis in the pulmonary circulation. The patient has loud breathing, prolonged inspiration and expiration; there is even an absence of the coarse, moist rales we find in the ordinary bronchial asthma.

François-Franck has shown by animal experiment two effects upon the lung from stimulation of the inner coat of the aorta at the valvular orifice and just above the vlave. The first effect was on the pulmonary arterial branches and the second on the bronchi. There is a reflex spasm produced in both. The spasm of the bronchi is assumed because there was an increase in the resistance to distension of the lung and an increased resistance to insufflation of air in the bronchial tract (this experiment was done on the curarized animal). François-Franck observed also in these

experiments cough and spasmodic closure of the glottis. The blood as a result of these experiments contained a diminished amount of oxygen and excess of carbon dioxide. There is a very striking consistency between the clinical picture of these cases of reflex paroxysmal dyspnœa and the animal experiment. Spasm of the bronchi and contraction of the pulmonary arteries would produce a dyspnœa with cyanosis without rales. Some cases of cardiac dyspnœa may be explained by François-Franck's theory, although it must be admitted that this explanation has not as clear an experimental basis as we would wish for such a common clinical experience.

Cardiovascular disease is attended with another form of respiratory distress, which is also quite independent of the gross hydraulics of blood distribution. It is very probable that many such instances are explained in many quarters by the intricate and ingenious theory offered by François-Franck, when, in reality, they are explainable on a much simpler basis. A man, aged sixty years, has occasionally awakened in the night (for the past three years) with intense air hunger which compelled him to sit upright in bed and breathe very deeply for a period of about five minutes. He did not have dyspnœa in an etymological sense. He suffered from air hunger and hyperapnœa. During his waking hours he never had any respiratory distress. For three months his wife observed that these attacks were always preceded by complete cessation of respiration. The patient had alternating periods of apnœa and hyperapnœa, the so-called Biot type. It was then observed that apnœa developed the moment he would go to sleep, and after about a minute of apnœa the patient awakened with intense air hunger and hyperapnœa. The wife then discovered that the period of air hunger and hyperapnœa did not occur if her husband was closely watched and awakened the instant the apnœa was apparent. For three months it was her practice to watch her husband as he went to sleep, and if apnœa ensued she awakened him instantly, for if spontaneous awakening was awaited the air hunger and hyperapnœa caused intense distress. As a usual thing the patient would have to fall asleep from five to twelve times before sleep could be procured without the supervention of apnœa. This patient had marked arterial sclerosis of the Gull and Sutton type, with the usual cardiac and renal signs. His systolic arterial pressure was 200 mm. Hg. The carotid pulse had a prolonged katacrotus, so that it was fair to assume there was extensive sclerosis in the brain arterial supply. There was a small margin of accommodation in the total bed of the brain arterial supply. Immediately on falling asleep there was sufficient anemia of the respiratory centre to render it hypo-esthetic, and apnœa persisted until the accumulated partial pressure of carbonic acid in the blood was sufficient to arouse the hypo-esthetic respiratory centre; whereupon, the patient suffered from air hunger until the partial pressure of carbonic acid in the blood was again reduced to its normal point. After repeated attempts at going to sleep the patient was able to procure sleep, which, however, was not so profound as he would have had if the apnœa had not interrupted it. His later sleep was not attended with the same reduction in the blood supply to his brain as attended the deep slumber

in the early part of the night. The slumber apnœa ceased promptly after the administration of nitroglycerin and citrate of caffeine.

Another patient with a similar experience had the Stokes-Adams syndrome and heart-block, with an arterial pulse rate of 30 and a jugular venous pulse rate of 120. For nearly five months it was necessary to watch this patient every night and arouse him every time he fell asleep, because apnœa developed immediately he went to sleep. It was not until the early morning hours that he could procure sleep without apnœa, and this sleep he said was very light. This patient had a syphilitic infection seven years before and showed marked sclerosis in all his accessible arteries. There were in this instance two possible sources of the slumber apnœa, viz., heart-block and sclerosis of the basilar arteries. Under prolonged and vigorous treatment with mercurials he recovered simultaneously from heart-block and slumber apnœa.

In medical literature we find frequent comments on nocturnal dyspnœa which awakens patients out of a sound sleep, but is unaccompanied by any signs in the lung or circulation to account for the respiratory distress. A notable feature of all these cases is arterial sclerosis with chronic aortitis; Huchard and François-Franck have seized upon this point as the source of a reflex vasomotor effect, as above described. In such cases we are really dealing with a bulbar symptom. If patients are closely watched we find slumber apnœa precedes the air hunger and hyperapnœa on awakening. Another fact in support of this view is the character of heart disease in which the Cheyne-Stokes and Biot types of respiration are produced after the injection of morphine. All these patients have arterial sclerosis and no doubt the bulbar arteries share in the process. There is a moderate depression of the respiratory centre not sufficient to cause apnœa, but if the added factor of morphine be supplied there is sufficient hypo-esthesia of the respiratory centre to produce either the Cheyne-Stokes or Biot respiration.

CHAPTER II.

DISEASES OF THE PERICARDIUM.

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PERICARDITIS.

Etiology.—Pericarditis occurs so rarely by itself that it can scarcely be regarded as a distinct disease. Independent infection of the pericardium probably never occurs except in those cases in which it is wounded either by penetration or contusion. A contusion of the chest may rupture small vessels in the pericardium, and thus render it liable to infection. From within the body the pericardium may be wounded by a foreign body, such as a needle or a spicule of bone lodging in the œsophagus.

Pericarditis is caused by infection conveyed (1) by the blood and (2) by direct extension. It occurs at all ages; even in the fetus cases have been reported. In the newborn infection may take place through the navel. By the way of the blood, infection may reach the pericardium in rheumatic fever, miliary tuberculosis, smallpox, influenza, septicemia, cerebrospinal meningitis, etc. Of these rheumatic fever is most frequently the source of infection. This was first pointed out by Pitcairn in 1788. From the ages of five or eight to twenty-five years, the rheumatic infection is especially prone to cause pericarditis. In later life it occurs most often in the course of Bright's disease, tuberculosis, and gout.

By extension it may be due to a great many causes, both in the chest and abdomen; such as pneumonia, pulmonary tuberculosis, pleurisy (simple and purulent), diseases of the mediastinal glands, aortic aneurism, acute and chronic endocarditis, especially of the aortic valves, peritonitis (suppurative), and other diseases within the abdomen, such as subdiaphragmatic abscess, cholecystitis, abscess of the liver and pancreas, gastroduodenal ulcer, suppurative appendicitis, etc.

While it is true that in exceptional cases the exudate is sterile, there is little doubt that the disease is always caused by the entrance of microörganisms of some kind. Those most usually found are the staphylococcus, streptococcus, tubercle bacillus, pneumococcus, meningococcus, and colon bacillus.

In *rheumatic fever* pericarditis usually becomes evident in the second week of the attack. Hughes met with it from the sixth to the tenth days; Sibson before the eleventh day in more than half his cases; and Bamberger up to the fourteenth day. Thus the occurrence of pericarditis at the height of the disease indicates that it is not a metastasis, but bears the same relation to the rheumatic infection as does the arthritis. Sibson found that its occurrence is not nearly so dependent on previous

rheumatic attacks as is endocarditis. There appears to be increased liability to pericarditis in cases of chronic endocarditis in which the heart is dilated and hypertrophied. In some cases the pericardial affection precedes by several days the articular manifestations. Such cases are reported by Graves, Stokes, Trousseau, West, and others. Males are much oftener affected with rheumatic pericarditis than females, but the greater liability of the male occurs probably only after maturity, and may be accounted for by exposure and overstrain.

Chorea is quite frequently associated with pericarditis, or more frequently still with endopericarditis. The cardiac affection may precede the choreic movements. There was pericarditis in 19 of 73 autopsies in cases of chorea collected by Osler; in only 8 of these was there a history of arthritis.

Pleurisy coexists with pericarditis very often, both affections being due to the same general infection, such as that of rheumatic fever.

Pneumonia is complicated by the secondary development of pericarditis usually in proportion to the severity and extent of the disease in the lungs. The danger of infection is least when an upper lobe is affected, and is much less when the disease is unilateral than when bilateral. Preble[1] says the liability to pericarditis in unilateral pneumonia is in the ratio of 1 in 40 cases; in bilobar and trilobar 1 in 10; and in quadrilobar 1 in 5. Pericarditis occurs more frequently in association with affections of the right lung than of the left. In 31 cases in Osler's service at the Johns Hopkins Hospital the right lung was affected in 13 cases, and the left in 5; both were diseased in 13 cases. Pneumococci were found in the pericardial exudate in 19 cases; in the remainder the exudate was sterile.

Gonorrhœal infection is not a rare cause of pericarditis. First pointed out by Fournier, it was later admitted by Ricord and Raymond. The gonococcus has been found in the pericardial exudates.

Tuberculosis of the pleura or the lung frequently precedes that of the pericardium. Tuberculous pericarditis may be a part of general tuberculosis, but more usually it develops subsequently to infection of the mediastinal glands, of the lungs and of the pleuræ. Cases have been met with in which the pericardium was the only part affected.

In *typhoid fever* pericarditis is a rare complication. In McCrae's series of 1500 cases it occurred only in 3.

Chronic nephritis is acknowledged by all observers to be a cause of pericarditis. Sibson[2] placed the average at 8.1 per cent.; this is probably a fair estimate. He found pericarditis rare in acute scarlatinal nephritis of young persons. It occurs most frequently in chronic diffuse nephritis and in contracted kidney. It is not rare in lardaceous disease. It may occur as one of the forms of "terminal infection."

Pathology.—The lesions of pericarditis may be limited to a part of the serous membrane—*circumscribed pericarditis;* more frequently it involves the entire pericardium—*diffused* or *generalized pericarditis.*

[1] *American Medicine,* June 15, 1901, p. 482.
[2] Reynolds' *System of Medicine,* vol. iv.

Circumscribed pericarditis is usually confined to the upper part of the pericardial sac, especially the cul-de-sac about the base of the aorta and pulmonary artery. It is generally limited to the anterior part, affecting first and chiefly the visceral layer, and later, to a less extent, the corresponding parietal layer.

Acute Pericarditis.—1. *Congestion and Fibrinous Exudate.*—The membrane presents a rose or red color, more or less intense, with a visible vascular network, and often minute ecchymoses, especially in young children. In the lightest degree of inflammation there occurs some increase of the ordinary pericardial fluid, which soon becomes somewhat opalescent from emigrated leukocytes and desquamated epithelium. The exudate seldom terminates with only these alterations, as the pericardium is easily stimulated to the formation of a high grade of fibrinous exudate. This occurs in the lighter cases as an oozing, which forms small granules on the surface of the pericardium, giving it an opaque appearance; the presence of the exudate is readily demonstrated by gently scraping the surface with the blade of a knife. If the inflammation is more severe, a greater amount of fibrinous exudate is formed. The pericardium becomes soft, thick, and, owing to the proliferation and destructive desquamation of its epithelial covering, assumes an opaque, velvety appearance. This phase is of very short duration, being soon followed by a fibrous exudate, which is at first easily detached from the serous surface, but soon becomes more adherent. It is semi-transparent, gelatinous, and yellowish in color. As new layers are formed, the exudate presents a stratified appearance and becomes thick and opaque; it may show, here and there, red areas from extravasated blood.

Owing to the movements of the heart, the surfaces of the exudate take on an irregular, papillated, or honey-combed appearance. Ridges may be formed, those on the surface of the heart having their counterparts on the parietal surface of the pericardium which is in contact with it. The surface has been compared to a variety of appearances: two patties of butter compressed together and then suddenly torn part (Laennec); tripe, or the second stomach of ruminants; honey-comb; the tongue of a cat, etc. It may, however, show a markedly villous appearance; hence the appellation *cor villosum* or *hirsutum*. If there is much fluid present the fibrinous exudate may accumulate in large processes and present a mammillated appearance. Occasionally these processes extend and become attached to the opposite pericardial surface, and, later, become organized into fibrous bands.

In most of the acutely infective cases, masses of microörganisms are found in the fibrous exudate.

2. *Liquid Exudate.*—In the great majority of cases of diffuse pericarditis, particularly in those due to rheumatic fever, there is a *sero-fibrinous* exudate. Usually it is not of great quantity—from 3 or 4 to 12 ounces (100 to 350 cc.); rarely more than a pint (500 cc.); but over 60 ounces (1800 cc.) have been found present. The exudate is usually clear, transparent, and straw-colored, but may be greenish; it may present small flakes of fibrin in suspension, or be more or less opaque

from the presence of leukocytes, *seropurulent;* or of red blood corpuscles, *serosanguinolent;* or in more extreme cases *purulent* or *hemorrhagic.*

Red blood corpuscles are frequently present in the exudate of tuberculous cases. Blood-stained serum has also been met with in *Bacillus coli communis* infection.[1] An excessive proportion of blood is rarely found except in purpura or scurvy, in which the quantity of effused blood may be very great, exceeding the quantity of effusion in any other form of pericarditis. Ryan reports having found as much as ten liters of fluid, chiefly blood, in scorbutic pericarditis. Hemorrhagic exudate occurs also in cancer, Bright's disease, alcoholism, and cachectic states. It is characterized by the presence in the liquid of a marked proportion of red corpuscles, or the deep stain of an abundance of blood pigment. The false membrane is also deeply colored. Some degree of hemorrhage is not rare in acute pericarditis of the aged, especially in arteriosclerosis. The hemorrhagic exudate of the eruptive fevers is to be regarded as the result of an extreme toxemia.

Purulent exudates are usually such from the commencement of the attack. The internal surface of the pericardium in purulent cases presents an ulcerated appearance, resembling a suppurating surface. The sac is in reality an abscess cavity, and the pus may penetrate the wall and burrow in any direction. It may discharge through an intercostal space or even above the clavicle, and form a pericardial fistula with or without pyopneumopericardium resulting.

Early in the inflammatory process in pericarditis the connective tissue becomes the seat of leukocyte infiltration. By the third or fourth day, on the surface of the pericardium, appear numerous proliferations of capillary loops which penetrate the deeper layer of the plastic exudate. In *the deeper* parts of the exudate, numerous polymorphonuclear leukocytes and large embryonic cells appear which in time are converted into new connective tissue. In the early period of this process the plastic exudate forms a grayish semitransparent layer with the new vessels appearing as red lines buried in its substance. With the development of the new connective tissue the plastic exudate is absorbed. If the inflammation is slight, the new tissue formation is scant and confined to a few small, white, thickened areas on the surface of the heart—maculæ tendineæ, or "milk spots." In some cases there are only a few spots, while in others they are numerous and occur on all parts of the surface of the heart and great vessels. Frequently thread- or band-like processes are found connecting the visceral and parietal surfaces.

If the pericarditis is marked so that there is abundant fibrinous exudate, and the inflammatory processes persistent so that there is much new tissue formation, the two layers of the pericardium may become completely adherent, obliterating the cavity—*adherent pericarditis.* In most cases the fluid and plastic exudate are absorbed, but some remnants may be left and become caseous or the seat of cretaceous deposit. In rare cases the new-formed fibrous adhesions of the pericardial surfaces become infiltrated with lime salts, forming large calcareous plates which may coalesce and inclose the heart in a hard, unyielding, *calcareous tunic.*

[1] Stewart, *Edinburgh Medical Journal,* 1904, vol. xv, 158.

In mild cases the inflammatory process is confined to the pericardium; in severer cases the pleura and mediastinal tissues may be involved and result in pleural adhesions and extensive *indurative mediastinitis.*

In certain infectious processes the exudate from the beginning is seropurulent. This is most likely to occur in pyemic cases, as well as in those of pericarditis secondary to purulent inflammation in the mediastinum, the pleura, and the mediastinal glands; also to ulcerative processes of the œsophagus, the stomach, etc., rupturing into the pericardium.

3. *Period of Absorption or Organization of the Exudate.*—After a time, in cases not terminating fatally, absorption usually occurs. Absorption of the serum may take place in a few days, leaving only the fibrinous part, which in some cases undergoes granulation and is absorbed; the epithelium is reformed and all traces of the affection are removed. More frequently the false membrane is long in being absorbed; beneath it granulation tissue is formed in which new vessels are developed, ending in the formation of new connective tissue. The opposing surfaces of the pericardium may become adherent over greater or lesser areas, and even universal obliteration of the pericardial cavity may take place.

Lesions in the Neighboring Tissues.—As already pointed out, inflammation of the fibrous tissue outside the pericardium often occurs, *mediastinopericarditis.* It may lead to the formation of adhesions and fibrous bands, more or less closely uniting the pericardium to the sternocostal surface and to the great vessels of the mediastinum.

The *cardiac* changes may be grave. The coexistence of endocarditis is frequent; it may precede or follow the pericarditis, the infection extending from one to the other serous surface by the lymphatic vessels, especially probably through the thin wall of the auricle, or through the walls of the large vessels; or both affections may arise at the same time and from the same pathogenic cause. *Myocarditis* is present in all cases of pericarditis, and chiefly to it are due the *dyspnœa* and circulatory disturbance, especially in the absence of large effusion.

Symptoms.—Owing to the multiplicity of forms, and the numerous modifications of the course of the disease of the same form of pericarditis, the symptoms present great variety. Further, they are often so masked by the associated diseases that pericarditis frequently runs its course without being recognized; in fact, it is not rarely the case that its existence even when sought for cannot be satisfactorily determined.

As a rule, there are general symptoms of constitutional disturbance, such as rise of temperature, frequent pulse, disturbed action of the heart, some dyspnœa with increased frequency of breathing, and a varying degree of precordial pain and distress. In children, disturbance of sleep may be the only complaint; there may be night-terrors and some delirium on waking. There is, in all cases, some enlargement of the heart from dilatation; it may be demonstrable in the earliest stage. But the only distinctive sign of pericarditis at its onset is the presence of a *to-and-fro friction sound.*

In view not only of the latent course in many cases, and the absence of definite symptoms in many others, but also of the frequency of the complete masking of the most characteristic phenomena by the asso-

ciated diseases, frequent examinations of the heart should be made in cases of rheumatic fever, pneumonia, nephritis, and heart affection. This is of especial importance, if, in any of the above-mentioned affections, there is sudden elevation of temperature, delirium, or any marked disturbance of the nervous system, especially in children, for which a definite cause is not apparent.

Pain is usually present; Sibson found it in 70 per cent. of his cases. In most cases it is diffuse in the thorax, with precordial oppression; it may be increased by movements, deep inspiration, and cough, and by external pressure. It appears to be due to the inflammation of the serous membrane, and, according to Babinsky, is always severe in children. It may be referred to the shoulder or the left scapular region, but oftener to the epigastrium, where, in some cases, it is very severe. In these cases the diaphragm is fixed and immobile. The late Dr. Barlow[1] directed attention to this as a valuable diagnostic sign, and reported the well-known case of the boy who tightly belted himself because he was relieved by preventing movement of the lower part of the chest and abdomen. There may be some immobility even in cases without pain or distress; with effusion the diaphragm is low and probably fixed in proportion to the quantity of fluid. Owing to contact of the pericardium with the œsophagus, the taking of food and drink may be painful. In many cases, besides diffuse tenderness in the precordial portions of the intercostal spaces, special tender points may be found in the course of the phrenic nerve, the first point above the clavicle between the two chief insertions of the stenomastoid muscle, and the second in the epigastrium between the costoxiphoid cartilage and the costal margin. Other points may be found in the intercostal spaces along the left margin of the sternum.

In certain cases pain, as described by Stokes, occurs in paroxysms like true *angina pectoris*. The pain begins in the precordium, extends to the left side, and is accompanied by numbness in the left arm, dyspnœa, palpitation, irregular action of the heart, anguish, tendency to syncope, and coldness of the extremities. The attacks have been attributed to extension of the inflammation to the cardiac plexuses and the phrenic nerve. They are of grave significance, not rarely terminating suddenly in death.

Dyspnœa is a frequent symptom. It may be due to pain, pericardial effusion, pleural effusion, and pulmonary collapse. To these should be added marked dilatation of the heart. In these latter, the dyspnœa is apt to be paroxysmal.

The *pulse*, in the early stage, is usually rapid, but otherwise unaltered. Later, as the blood pressure falls it becomes irregular and may be dicrotic. In some cases with large effusion there may be a manifest *pulsus paradoxus*.

The *temperature*, in most cases, is moderately elevated, especially in young persons. In chronic nephritis, and in cases with old-standing cardiac lesions, it may be only slightly elevated, but more often is normal or even subnormal.

[1] *Medical Times and Gazette*, September 5, 1857.

Sleep is usually disturbed by the pain and restlessness. *Cough* is not uncommon. It is short and dry, similar to that occurring in pleurisy. An anxious and distressed expression is frequent, even in the absence of pain. It is probably indicative rather of myocarditis than of pericarditis. Occasionally there is vomiting and hiccough. The voice may be altered, even lost, probably from pressure on the left recurrent laryngeal nerve.

Physical Signs.—In the first stage, inspection and percussion give no results unless the diaphragm is immobile on account of the irritation of the pericardium. Later, with effusion (4 ounces or more), there may be some fulness of the precordial area if the chest wall is resilient; this is, therefore, rarely seen except in children and in young adults. In persons of more advanced age the appearance of prominence is due chiefly to fulness of the intercostal spaces arising from paresis of the intercostal muscles caused by prolonged pressure, or extension to them of the inflammation.

Pericardial friction is the sign of greatest value in that it indicates the rubbing against each other of the two roughened pericardial surfaces. It was first heard by Laennec, who likened it to the creaking of a saddle; but it was not properly interpreted until described by his assistant, Collin, in 1824. The friction sound or vibration occurs in both the systolic and diastolic movements of the heart, hence designated as being a to-and-fro sound or vibration. It is usually heard first at the base of the heart, less often along its left border, over the lower end of the sternum, or at the apex of the heart; later it may become general over the whole surface of the heart, but more often extends gradually toward the apex, in the meantime disappearing at the base.

The character of the sound varies; it may be soft like rubbing of tissue paper, or harsh like the creaking of new leather or like the noise of scraping or scratching of rough paper, especially in chronic cases. It is superficial, and may even seem to pass between the thoracic wall and the ear of the observer. It may be increased by firm pressure with the stethoscope; Gibson pointed out that, if the pressure is too heavy, it may be weakened or even arrested, especially if the heart is weak. It is usually increased when the erect position is assumed and lessened in the recumbent posture. Exciting the heart's action may also increase it.

The duration of the friction sound is variable, in some cases lasting but a few hours, and in others throughout the greater part of the course of the disease. Its disappearance may be due to (1) absorption of the exudate on the pericardial surfaces; (2) adhesion of the opposing surfaces, or (3) increase of the exudate, plastic or serous. If the heart be held against the wall of the chest by adhesions or other cause, the friction sounds may persist even after copious effusion. When the exudate is absorbed the roughened pericardial surfaces again coming into contact may cause a recurrence of the friction.

It is almost pathognomonic, as the pericardial change necessary to produce it is almost always a dry pericarditis. In some cases non-inflammatory dryness or loss of smoothness of the serous surface, ecchymoses of the serous membrane, and "milk spots," may cause a pericardial

friction sound, especially if cardiac hypertrophy increases the energy of the heart's contraction, as was shown by Stokes and Graves.

The *respiratory movements* have a variable influence on the area and intensity of the friction sound; in some cases it is loudest in expiration, in others in inspiration. Its area is often increased below during inspiration and less often above in expiration (Sibson). An important characteristic is that it is almost always limited to the precordial area. There are some exceptions to this, however, especially during the decline of effusion; Sibson, in one case, found the friction sound audible over the greater part of the front of the chest, especially downward.

The *fremitus* or *vibration* of friction, if marked, may be felt by the hand placed on the precordium. It is felt as a peculiar vibrating or scratching sensation, usually when the sound is loud and rough, and gives the impression of being quite superficial. It lacks the vibratory character of the thrill of mitral stenosis.

The Heart.—In many cases the heart is disturbed out of proportion to the severity of the attack. In children the precordial impulse may be diffuse, heaving, and tumultuous, and show visible pulsation in the second and third intercostal spaces due to the auricular contractions; the right ventricle may be dilated and cause pulsation in the costoxiphoid angle. These phenomena frequently occur in protracted cases, in which cardiac dilatation is usual and often marked. In the *general circulation*, and especially in the *pulse*, there is sometimes marked disturbance, but it is not characteristic. In some cases the heart is irritable and the pulse very rapid, 120 or more per minute; probably the myocardium is rather extensively involved in these cases. As a rule the respiration is more greatly disturbed than the circulation.

Pericarditis often terminates in the dry stage with absorption of the exudate, or the adhesion of the opposing pericardial surfaces. In most cases, however, *serous effusion* takes place. In this stage the dangers are from two sources: the *abundance of effusion*, and the *degree of degeneration in the myocardium*.

The *pain* of the initial stage usually abates gradually, but may be succeeded by a distressing sense of constriction, or of precordial oppression which increases as the exudate accumulates, distends the pericardium, and compresses the heart. *Dyspnœa* from the same cause becomes marked, and may occasion much distress, especially if the effusion is rapid. The causes of the dyspnœa are multiple. The distension of the pericardium causing compression of the lungs, especially of the left, interferes with the movements of respiration and, by pressure, impedes the flow of blood through the heart, especially through the thin-walled auricles.

Venous stasis, chiefly in the pulmonary vessels, occurs and contributes materially to the increase of the dyspnœa, which may be marked by paroxysmal attacks and great anguish; in that case the face becomes cyanosed and swollen. When the effusion is large the erect position may give some relief, owing to the liquid collecting in the inferior part of the pericardial sac, thus lessening the pressure on the auricles and great vessels.

The effect of the pressure on the ventricles by the effusion will depend upon the degree of myocarditis existing; when the myocardium is seriously involved there may be danger of syncope.

Dysphagia may result from pressure of the distended pericardium on the œsophagus; in rare cases, aphonia is caused by pressure on the recurrent laryngeal nerves.

Effusion.—The friction fremitus, if present in the dry stage, will usually have disappeared. The cardiac impulse will be feeble, displaced, and later lost altogether; it will be diffuse if the heart is much enlarged, but if the dilatation is extreme the heart's contraction may be so feeble as to communicate an impulse only to the small area of the chest over the central part of the heart's surface. In such cases the heart extends far to the left of the area of impulse, and there may be much difficulty in differentiating dilatation from pericardial effusion. The impulse may reappear on lying down, especially in the prone position, the heart falling against the wall.

The area of *precordial dulness* affords important evidence of effusion. According to some observers the presence of one or two ounces of fluid suffices to appreciably alter the area of dulness, but many regard the existence of ten to fifteen ounces as necessary to make the diagnosis of its presence possible. With this and greater quantities, Sibson found the transverse diameter of the dull area at the third costal cartilage, corresponding to the pericardium covering the great vessels, relatively narrow; below this lies the heart, and the left border of the area of dulness is reflected rapidly outward, forming an obtuse angle, sometimes known as Sibson's notch. Dulness may extend to the right of the sternum appearing first in the fifth intercostal space on account of the accumulation of fluid in the pericardial process that normally extends into this part and becomes distended early in the attack. Dulness in this area has therefore been regarded as diagnostic of effusion (Rotch; Ewart). The extension of dulness being greatest in the fifth intercostal space and lessening as it ascends, converts the comparatively sharp angle between the right margin of precordial dulness and the upper border of liver dulness into a broad obtuse one. But Broadbent[1] has, in several instances, found dulness in this area in cases in which post-mortem the heart was found dilated and the pericardium adherent, but without the presence of fluid.

Lee[2] pointed out that rheumatic fever produces, apparently in all cases, dilatation of the left ventricle with frequently diffusion and weakening of the impulse of the heart and enfeeblement of the first sound. In the mildest cases of rheumatic fever the precordial dulness hardly ever fails to reach the nipple line; it usually extends a finger's breadth beyond it and may go farther without any murmur.

The extension of dulness beyond the site of the cardiac impulse has been regarded as quite distinctive of effusion, but such extension of dulness without perceptible impulse may be due to dilatation in which there is marked weakness of the heart's contractions. Ewart has drawn

[1] *Encyclopdeia Medica*, vol. ix, p. 283
[2] *British Medical Journal*, November 21, 1903, p. 1319.

attention to the occurrence of dulness at the base of the left lung close to the spine in cases of large effusion.

Fitz[1] reported a case of intrapleural lipoma about the size of a newborn child's head, which occupied the anterior and inferior part of the left pleaural cavity and obscured the diagnosis of a purulent pericarditis.

Auscultation shows, especially in the dorsal position, enfeeblement, and later, as a rule, disappearance of the friction sound, and weakening of the heart sounds, which to the ear appear distant and flapping. In compression of the lung from large effusion there will be signs simulating pleural effusion; dulness, loss of vocal fremitus and of the vesicular murmur; there may be œgophony, especially in the left mammary region and over the dull area below the left scapula, usually more marked in the dorsal decubitus, but lessening or disappearing in the genupectoral position.

Stage of Absorption.—The pericardial inflammation may terminate early and the exudate be completely removed, the pericardium being restored to a normal condition; or the lesion may persist for a longer or shorter time and terminate in chronic pericarditis. If the exudate is rapidly absorbed, the physical signs of the first stage may all return, but in the reversed order.

The Forms of Acute Pericarditis.—*Pericarditis Sicca.*—In many cases pericarditis remains dry throughout its whole course; it may be localized or general. It produces little disturbance.

Serofibrinous Pericarditis.—This is the common form; its first stage presents the same symptoms as the dry form. It occurs frequently in rheumatic fever and coexists quite often with endocarditis. It may be a primary lesion, as after exposure to chill, or from pneumococcic infection, as well as secondary, especially in the course of pleurisy, pneumonia, and Bright's disease.

Purulent Pericarditis.—This form may be a primary lesion, but more frequently it occurs in the course of pyogenic infectious diseases. A serofibrinous effusion may become purulent. In addition to the ordinary signs of pericardial effusion there is protracted fever of a septic character. The pulse and heart's action are weak on account of the infection of the myocardium. The course is usually short, it may be only two or three days in terminating fatally; recovery is rare.

Hemorrhagic Pericarditis.—This form presents no especial phenomena to indicate the character of the effusion. It may occur in the course of cardiac affections and injuries, Bright's disease, carcinoma, tuberculosis, alcoholism, and in the aged. In most cases the exudate is a blood-stained serum in which leukocytes are moderately numerous; the fibrinous exudate is usually scant. The pericardium is deeply stained with blood pigment. The red blood corpuscles are at first intact, but soon break down, and the coloring matter set free is diffused in the serum. Small extravasations into the pericardium are frequently found. In the hemorrhagic eruptions of fevers and scurvy the prominent feature is the cardiac weakness with collapse and syncope; sudden death is usual. If the hemorrhage is abundant, there will be phenomena analogous

[1] *Transactions of the Association of American Physicians*, vol. xx, p. 57.

to those in other free internal hemorrhages; vertigo, oppression, cold sweat, small, weak pulse, faintness, cold extremities, and death more or less sudden.

Chronic Pericarditis.—The chronic affection is ordinarily the sequence of an acute pericarditis in which recovery has been arrested in the course of the absorption of the exudate. In certain cases the affection develops so imperceptibly as to merit the appellation when first discovered particularly in the aged, in chronic nephritis, in the tuberculous, alcoholics, and the debilitated. When chronic pericarditis succeeds the acute form it is characterized by the persistence of the physical signs; stationary or gradually diminishing effusion, which may increase from time to time with a return of the acute symptoms, and signs of increasing myocardial degeneration, especially in the circulation becoming more and more defective. The pericardium may become in time adherent over its whole surface and the case thus terminate in *adherent pericardium.*

Course, Duration, Termination.—It is impossible to give more than approximately the duration of acute pericarditis as it presents multiple forms, very variable intensity, and, in its general course, is much affected by the infectious disease with which it is associated. In the adult it is usually acute and the symptoms severe; in children it is more often subacute and insidious in its development, and frequently runs a long course, terminating in adhesion of the two layers of the pericardium.

In mild cases of dry pericarditis, even although the general symptoms are marked, the friction rub may disappear in a few days, and convalescence may be rapid. Even with moderate serofibrinous exudation the recovery may be as rapid, but this is rare. If the pericarditis is severe death may take place within a few days after the onset, but this is unusual. This is not due to the pericarditis but to the myocarditis; at the autopsy there is found a moderate exudate of lymph on the pericardium, giving rise to a shaggy appearance of its surface, and the heart is greatly dilated, and its structure in a state of extreme, acute degeneration. The onset of pericarditis in rheumatic children is usually insidious, and when first examined both apical systolic murmurs and friction sound may be present. The friction rub may persist for days or even weeks, the area of precordial dulness in the meantime becoming greatly enlarged from cardiac dilatation. Pericardial adhesion may gradually take place and the heart never regain its normal size and vigor.

Diagnosis.—The existence of pericarditis is very frequently overlooked. Its course in many cases is so insidious and the signs so indefinite that its existence is not suspected, and a careful examination is therefore not made; and also because it is so often associated with other diseases, especially pneumonia, which overshadow its symptoms and frequently so obscure it as to make a diagnosis impossible, or, at most, only probable. Such symptoms as pain in the precordium, the tender points along the course of the phrenic nerve already referred to, the quickened respiration, anxious countenance, and venous stasis may indicate its occurrence, but then most of these symptoms may be present also in pneumonia, in diaphragmatic pleurisy, in endocarditis, and especially in myocarditis.

The one physical sign that is practically characteristic is the friction

rub. There are many cases, however, in which it is not found; it may be slight, last only a few hours, and disappear before an examination is made, or occur only between examinations. But once distinctly heard it can scarcely be confounded with anything else. Difficulty may arise in cases of dry pleurisy affecting the pleura in immediate contact with the pericardium; in such a case the cardiac movements may cause a pleural friction rub and as it is synchronous with the movements of the heart, it closely simulates pericardial friction. The pleuritic rub is more modified by respiratory movements, and is audible only over the left border of the heart and not over the sternum or base of the heart. Furthermore, a pleurisy is seldom confined to this area, but extends outward over the lung into the axilla. It is also usually intensified by deep expiration, and weakened or quite lost in inspiration. In pericardial cases the distinctive character of the rub is probably usually accentuated in inspiration.

In mild subacute attacks of pericarditis, especially in children, the onset is so insidious that the disease may exist for some days and the heart have suffered serious damage before the child is considered to be seriously ill, and even then it is only after a careful examination, in which the signs of pericarditis are sought for, that the actual condition is recognized.

Endocardial murmurs are usually easily distinguished from the pericardial friction rub, and the diagnosis presents no difficulty; but in the ill-defined cases of either disease, and in the cases in which they co-exist, the differentiation is frequently impossible. Endocardial sounds have a point of maximum intensity from which they are propagated to some distance, while the pericardial sounds are usually definitely localized in a very narrow area around the point of production. Respiration and the posture of the patient, as a rule, greatly alter and often obliterate the pericardial friction sound; usually they have much less influence on endocardial murmurs.

The diagnosis of *pericardial effusion* from cardiac *dilatation* frequently presents great difficulties. Effusion is indicated by dulness extending beyond the point of cardiac impulse, to the right of the sternum, especially in the fifth intercostal space, and upward above the third left costal cartilage. It occurs most rapidly and extensively in the severe and acute cases, and is marked also in the late stage of subacute and recurrent ones. It is greatest in children, in whom also it is more easily demonstrated on account of the thinness of the chest wall and absence of emphysema, and in them it may cause fulness of the precordial region. The existence of Sibson's obtuse notch, already described, if demonstrable, is of much value. The boundary of the dulness of effusion is usually more abrupt than that of cardiac enlargement, and the transition from the flat note over the effusion to the resonant one over the lung is usually sudden. Change in position and shape of the dulness with change of position of the patient is a valuable sign if it can be definitely made out.

Increasing weakness of the cardiac impulse until it finally is completely lost, with growing enfeeblement of the sounds of the heart, and, at the same time rapid increase in the area of precordial dulness, are strongly

indicative of pericardial effusion. With large effusion there is usually marked increase of precordial oppression, fulness of the veins of the neck, cyanosis; a small, irregular, feeble pulse; distressing dyspnœa, and even orthopnœa.

There are many cases in which a differentiation of dilatation from effusion is quite impossible. In pericarditis, with only plastic exudate, the myocardium may be so profoundly involved that great dilatation develops rapidly, the sounds become very indistinct, the impact of the heart against the chest wall barely perceptible, and that only at its most prominent part and not at its left border, so that the dulness extends well to the left of the impulse and to the right of the sternum. The general symptoms become very marked, such as urgent dyspnœa; anxious, pallid facies; turgid, pulsating veins at the base of the neck; cyanosis; small, feeble pulse, and profuse perspiration. Error in diagnosis has led the most experienced observers to perform aspiration for the removal of fluid that did not exist; they have punctured the right ventricle, but fortunately without any injurious effect.

Even paracentesis does not necessarily determine the presence or absence of fluid in the pericardium; the heart may lie in front of the fluid and prevent access to it. Shattuck[1] met with several interesting cases apparently of this nature. In a young man, under the care of the writer, suffering from a very severe rheumatic pericarditis, apparently with much effusion, precordial dulness extended upward to the second rib, to the left to the midaxillary line, and to the right beyond the sternum 5 cm. in the fifth, and 3 cm. in the fourth intercostal space. He had frequent severe attacks of dyspnœa. Aspiration was tried in the left costoxiphoid angle, in the right fifth intercostal space, and in the left fourth intercostal space, first close to the sternum, and then an inch internal to the left margin of precordial dulness, but all were dry, although the needle entered the pericardial cavity in each instance; it came into contact with the heart in the first and the last two instances only after passing through an exudate from half an inch to an inch in thickness. There was marked dulness and loud blowing breathing at the angle of the left scapula, over the area described by Ewart as indicative of massive pericardial effusion. Improvement began a few days later; the area of precordial dulness diminished and the blowing breathing heard posteriorly rapidly disappeared. It seems probable that all the signs were due to extreme dilatation of the heart and copious plastic exudate. This view is supported by the rapid disappearance of the dulness posteriorly, as the heart contracted after digitalis was given freely.

Effusion into the left pleura may simulate pericardial effusion, and vice versa, especially if the pleural fluid is encysted in the neighborhood of the pericardium. The shape of the dull area, the condition of the lung, the position and character of the cardiac impulse, and the tone of the heart sounds should suffice to differentiate the two conditions. The coexistence of both pleural and pericardial effusions may be more

[1] *Transactions of the Association of American Physicians*, 1897, vol. xii, 183.

perplexing, but the signs peculiar to each are sufficient, as a rule, to guide to a correct diagnosis.

Affections accompanied with induration of the lung overlapping the heart, tumors in the mediastinum, and aneurisms of the aorta, increase the area of precordial dulness, but are distinguished from pericardial effusion by the form and topography of the dull area, and other symptoms and signs of the conditions.

In the determination of the *nature* of the effusion, the physical signs afford no assistance; the general phenomena, such as the course of the temperature, the general condition of the patient, the coexisting affections, and, above all, the cause of the disease, may furnish indications sufficient to decide whether the exudate is serofibrinous, purulent, or hemorrhagic. But in the majority of cases a positive diagnosis can only be made by withdrawing some of the fluid. The character of the infection on which the pericarditis depends does not necessarily determine the nature of the exudate. Thus, in tuberculous cases the exudate may be serous or hemorrhagic; in rheumatic cases it is usually serous, but may be purulent; and in septic cases, although usually purulent it may be serous.

Prognosis.—"Pericarditis, like other acute inflammations occurring in an otherwise healthy individual, may be expected to run a favorable course if not unduly treated" (Balfour).

The prognosis of simple, acute pericarditis without complications is favorable; the graver prognosis of the older authors is to be attributed to their estimate of pericarditis. As the pericardium is not a vital structure, its inflammation can be dangerous only as (1) it affords a large surface for absorption of toxic products; (2) the inflammation extends to the heart muscle; and (3) the effusion, by its volume, compresses the heart and impedes its diastole. Of these dangers the second is much the most frequent and grave, and it is this that makes pericarditis the most frequent cause of death in rheumatic fever.

In most severe cases the signs of dilatation and disturbed action of the heart occur so early that infection of its tissue must take place simultaneously with, or very soon after, that of the pericardium. The prognosis, therefore, depends chiefly on the extent to which the cardiac tissue is involved, and this is fairly indicated by the degree of dilatation and disturbance of the action of the heart. As in endocarditis, the younger the child the greater is the liability to pericardial infection in rheumatism, also to invasion of the heart muscle, so that age greatly influences the prognosis. In advanced age the outlook is also grave.

Much depends on the associated diseases. Acute endocarditis and pneumonia add greatly to the danger, chiefly from the greater liability to degeneration of the heart muscle. The association of chronic nephritis also adds greatly to the gravity, as does also tuberculosis as the exciting cause of the pericarditis. The nature of the effusion has much significance, the prognosis being much more grave when it is purulent or hemorrhagic than if it is serous.

Treatment.—The therapeutic indications vary according to the form of pericarditis, the period of its evolution, the chief phenomena presented,

and the accidents which complicate its course. It is important to appreciate the fact that the danger arising from pericarditis is rarely due to the inflammation of the serous membrane itself, but, first, to the pressure of the accumulated effusion hampering the action of the heart, only an occasional danger, and, secondly and chiefly, to the occurrence of inflammation in the wall of the heart itself, probably from simultaneous infection rather than from extension from the pericardium.

The treatment may be reduced to two general principles: to combat the inflammation of the pericardium, and to prevent the failure of the heart.

In counteracting the inflammatory process, especially in acute pericarditis, local applications to the precordial region are of chief importance. Various revulsants have been long in use, such as local bleeding, leeching, hot applications, sinapisms, the actual cautery, and a series of small blisters. These measures usually quickly relieve the thoracic pains and distress. The application of cold over the precordial area by means of compresses or icebags has become increasingly general in recent years. It usually relieves pain and steadies the action of the heart so that the application is not only well borne but comforting to the patient. The repeated application of a series of small blisters has been strongly advocated by some writers, especially by Caton. The application of two or three leeches to the precordium has proved useful in many cases, especially when there is pain.

The salicylates, which usually have such marked beneficial effect in the rheumatic fever of adults, are generally regarded as having little, if any, beneficial effect on the inflammation of the heart or its membranes, endocardial or pericardial, and as liable to cause dangerous depression of the heart if given freely, especially in pericarditis. Lee strongly combats this. He attributes the cardiac weakness and dilatation to the effect of the toxin of rheumatic fever on the heart muscle, and not to the salicylates. There is much truth in this contention; but it is also apparently true, unfortunately, that once the cardiac structures are infected the salicylates have little influence in checking the infection. The same observation is nearly as true regarding joint infections. In both cases the salicylates, if given before infection of the cardiac and joint structures, respectively, and in sufficient doses, will probably prevent the infection or at least lessen its virulence. Care should be taken that the salicylate of soda is pure; about 20-grain (1.3 gm.) doses with an equivalent or even double the quantity of sodium bicarbonate or citrate should be given every two hours to the adult until the fever and pain are moderated, when the intervals may be increased to four hours, and, after a few days, the dose gradually reduced.

If the local applications fail to give relief to the pain, restlessness, and dyspnœa, opium or morphine may be given with much benefit. During the acute stage if stimulants are required, ammonia, alcohol, caffeine, strychnine, and strophanthus should be given, and not digitalis, lest it cause too great a strain on the injured heart by increasing the blood pressure. Quinine, given in an effervescent draught of bicarbonate of soda or potash, is a useful remedy. If the depression is marked and there is a

tendency to syncope, caffeine subcutaneously usually proves an efficient cardiac stimulant. The pure alkaloid is the most reliable, and with the addition of 1 or 2 grains of salicylate of soda, as much as 5 grains (0.3 gm.) can be dissolved in a hypodermic syringeful of water; the injection may be repeated frequently in urgent cases. It is often more efficacious than even large doses of digitalis, and is free from danger; but in some cases it causes nervousness and prevents sleep. Diuretin (theobromine salicylate) is an excellent cardiac stimulant and diuretic in many cases; it may be given in about 15-grain (1.0 gm.) doses three or four times daily. Theocin sodium-acetate, in doses of 3 to 8 grains (0.2 to 0.5 gm.), often proves a better diuretic. Atropine is sometimes of value; it should be given freely enough to cause a slight physiological effect.

If the dyspnœa is the result of pulmonary congestion and does not yield to local applications to the precordium and to internal stimulation, recourse should be had to venesection. The more quickly the blood flows the greater will be the fall of pressure in the right ventricle, and therefore the greater the relief.

In severe cases of rheumatic cardiac inflammation in children, nothing seems to have any influence on the progress of the disease, the course of which is usually rapidly progressive to a fatal termination. It is therefore important that children showing any indications of rheumatism should be promptly put to bed so as to be quiet and warm. The heart should be carefully examined from day to day, so that the most effective treatment may be resorted to at once on the first signs of involvement of any of the structures of the heart. The salicylates should be given freely, with large doses of bicarbonate or citrate of soda; children bear the drug well.

Pericardial effusion, if moderate and the heart shows no signs of embarrassment, requires no special treatment, since, as a rule, it is soon absorbed. The patient should be placed in bed, so as to relieve the heart of work as far as possible. If the effusion persists, absorption may be aided by repeated small blisters to the precordium, by diuretics, and saline purgatives. In all cases, common salt should be excluded from the diet, which should also contain little liquid.

If these measures have little effect, and in all cases of large effusion, especially if there are signs of cardiac disturbance, *paracentesis* should be done without undue delay, as death from syncope is liable to occur. It should be borne in mind, however, that the cardiac embarrassment is, in most cases, due chiefly to disease of the myocardium and the consequent dilatation, and usually only slightly, probably in most cases not at all, to the pressure of the effusion.

Paracentesis of the pericardium was first proposed in 1649 by Riolan, and afterward by Senac in 1794. The operation was very slow in being recognized as justifiable, not to say advisable; as late as 1870, Billroth characterized it as a prostitution of surgical skill. Various sites are recommended for puncture, the fourth or fifth left intercostal space near the sternum being the ones most often selected; next to these in the same spaces outside the nipple line and within the line of flatness

on percussion. A third point, and, if the diaphragm is depressed, probably the best, is high in the angle between the xiphoid cartilage and the left costal margin, the needle being directed backward until it has penetrated as far as the posterior surface of the costal cartilage and then turned sharply upward and to the left behind it; it should at once enter the cavity of the pericardium. The failure to obtain fluid does not necessarily prove its absence. A "dry tap" may be due to the plugging of the needle as it passes through the plastic exudate, to plugging by thick flakes of fibrinous exudate, or failure to enter the cavity containing the fluid.

The fifth right interspace, about an inch from the sternum, has been selected when this area is decidedly flat; it is probably not so uniformly satisfactory as the other points. An exploratory puncture with a hypodermic syringe is advisable to demonstrate the presence of fluid; but the fluid may not be reached by the hypodermic needle if there is much fibrinous deposit on the pericardium. A small aspirating needle should be used, the greatest care being taken to insure an aseptic operation. If a small incision be made through the skin the needle can be inserted much more easily, as it is not then grasped by the elastic subcutaneous tissue. After the aspiration the wound should be sealed by a suitable dressing.

Reaccumulations of effusion will necessitate repetition of the aspiration. In some cases as many as ten aspirations have been made, with ultimate recovery as far as the pericardial effusion is concerned. Charton punctured thirteen times, in a man aged forty-six years, for hemorrhagic effusion, but a final relapse was followed by death.

For purulent exudations free drainage will be required. The incision is usually made in the fifth left intercostal space close to the sternum. If there is insufficient room for drainage a semilunar portion of the costal cartilage may be cut away, also a portion of the margin of the sternum. At this point the pericardium is easily reached by carefully dissecting down to it, and there is no danger of wounding the pleura.

The injection of formalin in glycerin in a 2 per cent. solution may sterilize the cavity, as it has been found to do in localized pleural exudates.

In *chronic pericarditis* medication is ordinarily quite powerless for good. Some benefit may result from prolonged use of vasomotor stimulants like cold and heat, or such revulsants as blisters, etc., to the precordial region, and from the employment of tonics such as quinine, iron, arsenic, and of good food and fresh air, especially in new and favorable surroundings.

The persistence and recurrences of effusion are to be met by dry salt-free diet, diuretics, repeated hydragogue purgatives, and, in suitable cases, paracentesis. The injection of 15 to 30 minims (1 to 2 cc.) of a solution of adrenalin (1 in 1000) may be as useful here as it has been found in pleural effusion.

ADHERENT PERICARDIUM.

Synonyms.—Symphyse cardiaque; synechia seu concretio pericardii.

Definition.—Adherent pericardium is, properly speaking, only the adhesion of the two layers of the pericardium resulting from divers forms of pericarditis, and, therefore, neither a disease nor an affection. Nevertheless, it presents such special clinical signs and has associated with it such intra- and extrapericardial lesions that it merits special description.

Etiology.—All varieties of inflammation of the pericardium, acute or chronic, may bring about the formation of adhesions and obliteration of the cavity. The adhesion may take place in the course of dry pericarditis, and after the absorption of effusion, especially if slowly absorbed; also in cases that present a number of successive subacute attacks extending over years. The inflammation may extend to the mediastinum and ultimately form a *chronic fibrous mediastinopericarditis*. In some cases the process begins in the mediastinum, as in acute or chronic inflammation due to disease of the bronchial glands, malignant tumors, tuberculosis of the lungs or pleura, pneumonia, aneurism of the transverse aorta, or from trauma. W. H. Smith[1] has studied a series of 62 cases all of which came to autopsy. He divided the cases into two groups. In the first (26 cases) there were no symptoms referable to the heart at the time of death; in the second (36 cases) cardiac features were present. There were not any children in the first group and the average age was higher. In the second group antecedent rheumatic infection was more prominent, endocarditis was more frequent, and the adhesions were more marked. There were 6 cases with a history of rheumatic fever in the first group and 22 in the second. The majority of the second group died below the age of forty. Adhesions and cardiac enlargement were both markedly less in the first group than in the second.

Pathology.—This comprehends the study, first, of the pericardial adhesions; second, lesions in the mediastinum from extension of an infective process which sometimes extends to the serous membranes on both sides of the diaphragm; and, third, the alterations in the heart itself and their consequences.

1. **Adhesions in the Pericardium.**—These may be partial or general. When adhesions form after pericarditis they begin between the auricles and the parietal pericardium where the great vessels pierce the latter to enter the cavity; partial adhesions occur rarely at the apex. The adhesion may consist of the close attachment of various-sized areas of the two serous surfaces, or the connection may be by bands or strands of connective tissue of varying length, shapes, and sizes, and more or less vascularized. The adhesions may be extensive and so arranged as to form loculi of various dimensions in which exudate may be encysted.

General adhesion is rare, and often more apparent than real, for the membranes can, in most cases, be separated easily.

The adhesions, partial or general, are at first soft and easily broken

[1] *Jour. Amer. Med. Assoc.*, 1913, lxi, 739.

down; in time as the granulation tissue becomes organized, they are formed of firm, resistant, fibrous tissue. The two layers of membrane may be so intimately united that in the fibrous layer formed it is impossible to find a trace of the original membrane. The thickness of the layer thus formed is, therefore, very variable; thick deposits are especially liable to occur in tuberculous cases. The greater part of the deposit is usually formed by the visceral layer. The thickness may exceed even that of the cardiac wall, which may be difficult to separate from the fibrous mass. In occasional cases the adhesions undergo cartilaginous or calcareous change. The calcareous change usually follows a purulent exudate which has been partly absorbed.

2. **Lesions of Neighboring Structures.**—These are frequent and consist of bands in the mediastinum which form adhesions joining the fibrous pericardium to the thoracic wall in front, the mediastinum behind, and the central aponeurosis of the diaphragm below. They are the result of chronic recurrent inflammation, develop slowly, and are various in extent. In occasional cases all the loose mediastinal tissue is replaced by a dense, fibrous mass enveloping all the organs in the mediastinum, the whole being intimately attached to the thoracic wall, the pleuræ, the spine, and the diaphragm.

If the adhesions are few in number, and not tense, they have little, if any, influence on the state of the heart. But if they are extensive and firm, and the myocardium has been infected simultaneously with the pericardium, important changes occur in the heart itself. These are due partly to interference with the heart's action by the adhesions, and partly to the degenerative processes in the wall of the heart. Many observers have found the heart enlarged from hypertrophy and dilatation, while others regard atrophy as the more usual change. There can scarcely be a doubt that the former change is the usual one, because in these severe cases of pericarditis the tissue of the heart can scarcely escape infection, and this will injure its tissue and weaken its power so that dilatation should occur before adhesions and fibrous bands have become sufficiently firm to prevent the dilatation. Later, hypertrophy will follow from the increased labor arising from the interference with its activity by the adhesions and bands unless their contraction interferes with the blood supply to the cardiac walls.

If the myocardium has been little injured by the infection, the conditions are favorable for hypertrophy, especially in the absence of valvular lesions; the hypertrophic changes will be most marked in young persons. In general debility from any cause, and especially in the cachectic and the tuberculous, the conditions are not favorable for hypertrophy, and a greater or less degree of atrophy is frequent. Valvular lesions are frequent, as endocarditis often coexists.

In rare cases an excessive degree of new fibrous tissue has been formed about the roots of the great vessels, and its subsequent contraction has led to narrowing, or even complete occlusion, of one or more of them. The vena cava, superior or inferior, is most often affected, but the pulmonary artery or the aorta may also be involved. The secondary

changes caused by these vascular constrictions are widespread and vary according to the vessel or vessels affected.

The condition may consist of:

1. Simple adhesion of the two layers of pericardium, partial or over the whole surface, occurs in most cases of pericarditis. In the absence of the production of considerable new fibrous tissue, such adhesions do not disturb the heart's action or affect its structure.

2. Cases associated with chronic mediastinitis leading to adhesions of the pericardium to surrounding structures: (*a*) the chest wall in front; (*b*) the pleura on each side; (*c*) the mediastinal contents behind; (*d*) the diaphragm below.

The condition, especially in early life, is a grave menace to the integrity of the heart, which may be greatly dilated and hypertrophied, or its blood supply impeded by constriction of the venæ cavæ. Traction by adhesions may tug on the arch of the aorta, adding to the labor of the heart by obstructing the flow of blood. If the adhesions are chiefly to the left ventricle there will be disturbance of the pulmonary circulation with dyspnœa, etc.; if to the right ventricle the systemic circulation suffers, hence enlarged liver, peritoneal and other dropsies. In such cases there may occur widespread proliferative inflammatory thickening of the various serous membranes, *multiple serositis* or *hyaloserositis* or *polyorrhomenitis,* and induration of various organs, especially of the liver, due to proliferation of its capsule. The symptoms so closely resemble those of ordinary cirrhosis of the liver that the term "*pericarditic pseudocirrhosis of the liver*" has been applied to it or, more frequently, "chronic universal perihepatitis." Chronic peritonitis and chronic pleuritis often coexist, the infection apparently spreading from the diaphragm in both directions. There is marked thickening of the peritoneum, especially over the liver, where it is often irregular, presenting a fenestrated appearance, the "iced liver," or "Zuckergussleber" (Curschmann).

Symptoms.—In a number of cases there is a history of long-continued and increasing disturbance of circulation and respiration which is usually attributed to associated valvular defects. In another group of cases, chiefly of chronic adhesive mediastinopericarditis, the symptoms simulate those of hepatic cirrhosis, ascites being marked and requiring repeated tappings.

Laennec, although slow to recognize the signs of pericarditis, had a clear perception of the importance to be attached to this affection. The pericardium is so loosely attached to the surrounding structures that simple adhesion, even if general, cannot hamper it materially. The disturbances to circulation so frequently existing are to be accounted for chiefly by the associated conditions. In the order of their importance they are: affections of the myocardium usually resulting from the same infection and occurring simultaneously with that of the pericardium; valvular affections; chronic fibrous mediastinopericarditis; and massive fibrous thickening in and between the layers of the pericardium, with, in rare cases, the deposit of calcareous concretions. Other causes, such as pressure of fibrous bands on the great vessels and multiple hyaloserositis, are of rare occurrence.

The general symptoms are those of circulatory disturbance and insufficiency; palpitation, tumultuous heart action, precordial oppression, dyspnœa, anxiety, syncope, cyanosis, etc. All these indicate disturbed function or insufficiency of the myocardium. There is no doubt that these symptoms, especially the dyspnœa and cyanosis, are largely dependent on the disturbance of respiration, owing to interference with the movements of the diaphragm by the mediastinal adhesions, as pointed out by Wenckebach.[1]

Physical Signs.—Systolic, rhythmical retraction in the lower part of the precordial area, when present, is the most important sign of adherent pericardium. *Systolic retraction* may be confined to one or more intercostal spaces in the area of cardiac impulse, or be more widely distributed, affecting several spaces and sometimes the epigastrium, or, if still more forcible, the costal cartilages and even the lower end of the sternum may be drawn inward. When limited to the intercostal spaces about the cardiac impulse, the sign is not of material value, as it is sometimes observed in connection with other lesions, as in pleural adhesion at the margin of the left lung without any affection of the pericardium; it also occurs occasionally without adhesions of any kind, especially over the the body of the heart.

The retraction of the costal cartilages, and sometimes of the sternum, is a sign of much greater value, but yet not pathognomonic. It is apparently due to the strong adhesion of the pericardium to the inner surface of the thoracic wall on the one hand and to the heart on the other, so that during the systolic contraction of the heart the chest wall is drawn inward. Intimate adherence of the heart to the diaphragm alone has been observed to cause retraction of the lower precordial region by traction on the attachments of that structure to the thoracic wall.

Depression in the precordial region may also be observed when cardiac adhesions offer an obstacle to the normal movements of the heart at the base and to the left. In such a case, especially if the base of the heart is fixed, the retraction and elevation of the point of the heart in systole and the pressure of the air cause depression of the intercostal spaces. Pleuropericardial or pleurocostal adhesions often exist, and by preventing expansion of the process of the left lung that overlaps the heart, they usually increase the precordial recession. Such pleurocostal adhesion is usually associated with some lessening of the tympanitic semilunar space of Traube.

Marked undulatory movement is sometimes observed over the precordial area beginning above and to the right and extending downward and to the left; it is a kind of rolling movement and may sometimes be observed also in the epigastrium. It must be remembered, however, that undulatory movements may be produced in dilatation of the heart by irregularity in the contractions of the various chambers without there being any adhesion of the pericardium.

Immobility of the diaphragm in its central part, or decided lessening of its movements, as shown by deficient epigastric movement, or by

[1] *Brit. Med. Jour.*, 1907, vol. i, 63.

x-ray examination, may be due to adhesion between the heart and diaphragm; it is more marked if the adhesions include the chest wall.

Systolic retraction of the tenth and eleventh intercostal spaces below the scapula—Broadbent's sign—is regarded as evidence of extensive adhesions between the heart and diaphragm. It is occasionally seen on the right side as well as on the left. Its occurrence is attributed to the powerful traction of a greatly hypertrophied heart on the diaphragm.

Diastolic collapse of the veins of the neck was regarded by Friedreich as a sign of much importance, but does not occur often. Broadbent has observed systolic collapse in the superficial veins on the anterior surface of the chest; he attributed it to the traction of fibres extending from the pericardium to the internal mammary veins dragging in and opening them during systole, and obstructing and causing sudden distension of these veins during diastole.

Kussmaul's sign, or swelling of the cervical veins during inspiration, is probably of little importance. It is supposed to be due to the existence of pericardial adhesions, which prevent the normal inspiratory dilatation of the right ventricle.

On palpation there is perceptible *enfeeblement* or, it may be, *disappearance of the impulse of the heart* in some cases of pericardial adhesion. It is not, however, distinctive of adhesion, as it may be present also in myocardial degeneration, in pericardial effusion, and when there are changes in the anterior border of the left lung. Owing to the adhesions, the position of the impulse of the heart does not, as a rule, alter with change of position of the patient or with respiration; when present this is a valuable sign. The upper limit of cardiac dulness may be fixed and show no change with respiration.

Durozoiz has insisted on the necessity of considering together the sign of retraction as observed on inspection, and the simultaneous shock of systole as observed on palpation as affording a diagnostic sign of much value.

Shock, synchronous with the heart's diastole, is perceived in occasional cases by the hand placed over the area of cardiac impulse. It is probably due to the rebound of the fibrous adhesions put on the stretch by the heart's contraction. By some observers it is regarded as pathognomonic.

The *pulsus paradoxus* is a sign of doubtful value. The pulse, if at all affected by respiration, normally becomes slightly fuller and stronger toward the end of expiration. The *pulsus paradoxus* grows weaker and smaller, and may even disappear in deep inspiration, regaining its usual volume at the close of expiration. It "is of value in the diagnosis of indurative pericarditis only when there is a concomitant inspiratory engorgement of the jugular veins, a symptom which indicates a stenosis of the jugular veins during inspiration" (Sahli).

On *auscultation* the heart sounds will be found weakened, except during the period of decided cardiac hypertrophy, when they are distinctly accentuated. In mediastinopericarditis, sometimes fine friction rales of a parchment-like character are audible along the margin of the lungs at their junction with the area of superficial cardiac dulness; if they persist during the cessation of respiratory movements they furnish strong

proof of the existence of pleuropericardial adhesions. A creaking sound over the body of the sternum is, in some cases, audible during up-and-down movements of the arms (Babcock). In some cases a bruit is heard resembling the harsh sound of a presystolic murmur (Hale White).

Wenckebach has drawn especial attention to the inspiratory difficulty often met with from adherent pericardium. The strong adhesions that form between the heart and root of the lungs on the one hand, and the wall of the chest and the central tendon of the diaphragm on the other, in mediastinopericarditis so anchor the diaphragm that it cannot descend, carrying the heart with it in inspiration. The capacity of the chest is thus not increased in its vertical direction. The lower part of the chest is also bound down, so that the inspiratory capacity has to depend on the lifting upward and forward of the upper part of the chest, and the lateral expansion of the lower parts.

In cases of "pericarditic pseudocirrhosis of the liver" and "multiple serositis," there is increasing dyspnœa and great ascites, and, later, dropsy of the lower extremities. There may also be effusion into the pleural cavities.

There may be a similar group of symptoms without chronic inflammation of the peritoneum; in these cases the pericarditic changes affect chiefly the portal circulation. In some cases there is genuine hepatic cirrhosis, the diagnosis from which is possible only when there is thorough appreciation of the symptom group, due attention being given not only to the history of the case but also to the cardiac signs of adhesions of the pericardium, such as systolic retraction, absence of apex impulse, immobility of the area of precordial dulness, and restriction of the expansion of the lower part of the chest in inspiration, especially on the left side.

Diagnosis.—In regard to diagnosis there are three classes of cases of adherent pericardium: (1) those in which the signs and symptoms are so significant that a diagnosis can be made with ease and certainty; (2) those in which, after a careful investigation of all the symptoms and signs in the light of the history of the case, a probable or often only a possible diagnosis can be made; and (3) a large class of cases in which there is no history, nor either symptoms or signs to justify even a suspicion of the existence of adhesion of the pericardium. This third class includes all cases of simple adhesion of the pericardial surfaces without material exudate between them, and in which there has been no extrapericardial inflammation to cause adhesion to surrounding structures.

In the first class the signs are so typical, or there is such a conjunction of them, as to render diagnosis quite certain. Such a case was that of a lady, aged thirty-five years, who had been engaged in mission work in China for some years, and who wished advice as to her fitness to return to work. Five years previously she had a severe and protracted pericarditis from which she made a slow and incomplete recovery, palpitation and dyspnœa on exertion persisting and growing gradually more pronounced. On examination, well-marked systolic retraction was found to occur in the lower precordial region, affecting the fifth and sixth costal cartilages and lower end of the sternum, but chiefly in the

intercostal spaces and the epigastrium between the left costal margin and the ensiform cartilage. There was no respiratory movement of the epigastrium. The area of dulness extended from the right margin of the sternum to one-half inch outside of the left nipple line, and was not altered by respiration or change of position. Palpation showed a systolic shock synchronous with the recession, but no diastolic shock could be perceived. There was, in this case, the history of such an attack as would probably cause not only adhesion of the pericardium, but also infection of the myocardium on the one hand, and of the pleura and mediastinal tissues on the other; none of the essential signs of the condition of chronic fibrous mediastinopericarditis were wanting.

In the doubtful class of cases a diagnosis can frequently be made if the possibility of the existence of the affection is not overlooked, and due consideration given to the symptoms and physical signs. In many cases the symptoms are out of proportion to the signs and may be accounted for by the occurrence of adhesions. The symptoms are those of failing circulation and dilatation of the right ventricle without adequate cause to account for it. If suspicion is once aroused, evidence may be found to render a probable diagnosis justifiable. A protracted history of recurrent pericarditis is significant; and, if the patient has been under observation, the progress of inflammation may have been shown by the appearance of friction rubs at various points from time to time, together with an increase of the area of precordial dulness which remains undiminished after the pericarditis has been relieved. In such a condition effusion must be excluded, and due allowance must be made for dilatation of the heart.

In adherent pericarditis with secondary pseudocirrhosis of the liver and general serositis, the diagnosis is often difficult, especially in differentiating it from ordinary hepatic cirrhosis. In the latter affection there is usually a history of a cause such as alcoholism or syphilis, while in adherent pericarditis and multiple serositis there is often a history of rheumatism with, in some cases, pericarditis, or an acute illness in which precordial pain, distress, and other symptoms which may have been due to pericarditis were present. In ordinary cirrhosis there are often gastric or intestinal hemorrhages and the dropsy begins as ascites, œdema of the lower extremities following later; in the pericardial cases the œdema may precede the ascites if the changes in the liver and serous membranes are later in developing.

Great dilatation of the heart without hypertrophy, and not due to affection of the cardiac orifices, nor to lesions of the lungs, kidneys, arteries, stomach, etc., is probably caused by adherent pericardium (Potain). This is especially true in young persons; in advanced years, chronic change in the myocardium is more likely to be a cause.

Prognosis.—This depends on the nature and extent of the adhesions and the degree to which the heart substance has been implicated in the inflammatory process. If the adhesion consists merely of agglutination of the two pericardial layers, however intimately, it scarcely causes any change in the condition of the heart or affects its functions. In more severe cases the myocardium is involved in the inflammatory

process. In most cases it is to the degenerative and fibroid changes resulting from the inflammation that the subsequent dilatation and failure of the heart are chiefly due. The action of the heart will be hampered by the new connective tissue and usually still more by the adhesions to surrounding structures, especially such as are unyielding, as the chest wall and diaphragm.

Adhesions acquired in early life, especially those resulting from rheumatic fever, are usually followed early by serious functional disturbances; the younger the child the graver and more rapid the development of the symptoms. Rheumatic adhesive pericarditis has been regarded as the usual cause of cardiac failure in children. The gravity of the condition is greatly increased by the liability to recurrences of the pericardial inflammation, and by the coexistence of endocarditis or valvular affection. The occurrence of adhesive inflammation of other serous membranes—polyserositis—and extension of the inflammation to the mediastinum greatly increase the gravity of the prognosis. When the signs of cardiac failure, such as anasarca and ascites, develop, restoration of cardiac competency is difficult to establish and a fatal ending usually comes within a few weeks or, at most, months.

The disappearance of the systolic retraction is of grave omen, as it indicates progressive enfeebling of the heart's energy. The failure of the heart to respond to digitalis indicates profound alteration of its muscular fibre, and adds to the gravity of the prognosis.

Death usually results from cardiac asystole, sometimes after the first, more often after a succession of crises; it may occur with symptoms of syncope or of an anginal attack.

Treatment.—This is purely symptomatic. All rheumatic attacks in children, however slight, should be carefully treated, rest in bed from time to time being especially observed in order if possible to prevent affections of the heart or its membranes. As already remarked, the salicylates are generally regarded as having little influence on rheumatic cardiac affections, besides having a dangerously depressing effect if there is infection of the myocardium; given, however, at the onset of the rheumatic attack, they probably shorten it and thus render a heart infection less liable to occur. Cold or hot applications, and, especially, small blisters to the precordium, often do much good. Digitalis in moderate doses, to stimulate a vigorous systole and so lessen the liability to adhesions, may do much good, and should be continued for long periods. Respiratory gymnastics, by stimulating the vigor of the heart's action, will also aid in lessening the tendency to adhesions.

Once the adhesion is established, the treatment has for its chief aim the development and preservation of the cardiac hypertrophy. To this end the heart should be guarded from overstrain. This calls for the intelligent coöperation of the patient, who should therefore be carefully instructed, without unduly alarming him, as to the dangers and how best to avoid them. Graduated systematic exercises recommended in valvular disease of the heart, judiciously used, should be of benefit in this condition.

The secondary effects from venous congestion of the digestive organs

and the kidneys require frequent periodical recourse to active cathartics to reduce fulness of the portal system. For this purpose nothing serves the purpose better than a blue pill, or 1 or 2 grains (0.06 to 0.13 gm.) of calomel at night, followed next morning by Epsom salts or an aperient water. Such a course necessitates careful examination of the patient from time to time. When compensation yields and the venous side of the circulation becomes overloaded, complete rest is called for. The blood should be depleted by hydragogue purgatives, and if this is not successful, by venesection. The diet should be nutritious and of small bulk so as not to overload the stomach.

Digitalis is often disappointing owing to the degeneration of the heart muscle. Caffeine, grains 2 to 5 (0.13 to 0.3 gm.); diuretin, grains 15 (1.0 gm.), and fluid extract of apocynum cannabinum, minims 2 to 10 (0.13 to 0.6 cc.) may prove useful. Strychnine may do good and is best given hypodermically. For pain and restlessness, morphine should be given; it is also the best tonic for an overstrained, irritable heart. Anasarca may require drainage.

In cases with marked systolic retraction of the costal cartilages and lower end of the sternum, operation to separate the adhesions more or less widely has been proposed by Delorme.[1] Brauer[2] has carried out a much more effective operation for the relief of the condition. The operation, which he designates "cardiolysis," consists in resection of the ribs and cartilages, and even the margin of the sternum, to which the heart and tissues about the pericardium are adherent. The periosteum, as well as the ribs and cartilages, is removed. The object is to convert the resisting chest wall in the *regio cordis* into a soft, yielding tissue, so as to allow the heart to contract with ease and the diaphragm to descend in inspiration, carrying with it the heart and the roots of the lungs. By this means not only is the heart relieved of much that hampered its action, but, by allowing the diaphragm to descend, the respiratory capacity of the chest is greatly increased. He showed two cases at the meeting of the International Medical Congress at Budapest in 1909; in one the result was excellent, in the other there was only moderate relief owing to the existence of valvular affection and much dilatation of the heart.

TUBERCULOUS PERICARDITIS.

Tuberculous pericarditis is relatively a rarer affection than pericarditis in the tuberculous. It is generally accepted that many cases of simple pleurisy with sterile exudate are due to tuberculous infection, and pericarditis with sterile exudate may likewise be as frequently due to the same cause.

Etiology.—It is only during the last fifty years that tuberculous pericarditis has come to be generally recognized as a definite disease. It has been observed at all ages. Duckworth met with a case in a child of five months, and Lejard in a woman at the age of eighty-eight. It occurs

[1] *Traité de Méd.*, viii, p. 62.
[2] *Arch. f. Klin. Chir.*, lxxi, Heft 1.

probably most often in young adult life, and in males more frequently than in females.

In common with other parts, the pericardium is affected in miliary tuberculosis. Apart from this general infection, tuberculous pericarditis may occur as a secondary infection. The view is becoming more and more widely accepted, that the lymphatic glands are always the first seat of tuberculous infection, and that the various organs and tissues subsequently infected are invaded by way of their lymphatic vessels. If this theory is correct, and it probably is so, the terms primary and secondary largely lose their significance. Osler is, therefore, probably quite correct in regarding as primary all those cases "associated only with caseation of the bronchial, or, particularly, the anterior mediastinal glands," as these glands are probably in all cases affected before the pericardium is invaded.

Tuberculous pericarditis developes secondarily to disease of the lung, pleura, sternum, vertebræ, peritoneum, or even the intestines. The reason for the rare, and usually late, invasion of the pericardium probably lies in its relatively scant vascular supply. In rare cases there has been penetration of the pericardium by a neighboring tuberculous gland.

Pathology.—In tuberculous pericarditis are found many of the lesions common to other forms of pericarditis, as well as some of the distinctive lesions of tuberculosis. The pericarditis may be of the *dry* form, or be accompanied by *effusion*. In the dry form the condition terminates nearly always in adhesion of the pericardial surfaces; in the form with effusion, adhesion may also occur after absorption of the exudate has taken place. The *effusion* may be serous, serosanguinolent, or frankly hemorrhagic, but is rarely purulent. The occurrence of even a small quantity of blood in the serum is of diagnostic value. The quantity of effusion is variable; it may not be more than demonstrable at the autopsy, or may be very abundant. Hudels reports a case in which there were 2 liters, and in a boy aged twelve, a patient of the writer's, 1400 cc. of serosanguinolent fluid were removed at the third aspiration.

In many cases, tubercles are not demonstrable postmortem; if present, they are often very small. They occur most frequently on the parietal layer along the course of the small bloodvessels. They are found most frequently beneath fibrinous exudate in the meshes of the new fibrous-tissue formation. Sometimes larger tuberculous masses are formed by aggregation of smaller deposits. Their external parts are grayish, while the interior consists of yellowish caseating masses. The deposits occur most frequently about the base of the heart. They may invade the myocardium and even penetrate its wall into the cavity of the heart, especially that of the auricle.

In the majority of cases there is a fibrinous exudate of variable degrees of thickness, deposited chiefly on the parietal pericardium. There may be excessive formation of new fibrous tissue, at first grayish and translucent, but later becoming white and firm, as it is converted into dense cicatricial tissue which intimately unites the pericardial surfaces. If the exudate is purulent it may become inspissated and converted into a calcareous mass.

Symptoms.—As a rule, the affection is quite latent throughout its whole course, and is only discovered at the postmortem examination. This is accounted for by the fact, in the first place, that the disease of the pericardium usually begins insidiously and runs a subacute or chronic course, and, in the second place, that the pericardial symptoms are generally overshadowed by those of lesions in other organs.

In acute cases there is usually a rapid effusion, and the symptoms are similar to those of acute non-tuberculous pericarditis: pain, palpitation, some fever, friction sounds, dyspnœa, and the signs of effusion. The acute cases are generally due to infection from an adjacent tuberculous gland; and if the gland is caseous, the effusion may become purulent and obscure its tuberculous nature.

In the majority of cases, the course is chronic, and other manifestations of tuberculosis, especially of the pleura, usually suffice to reveal the nature of the pericarditis. Large effusion is exceptional, but if it is so great as to necessitate aspiration, and the fluid proves to be hemorrhagic, it affords strong evidence of the tuberculous nature of the affection.

The two layers of the pericardium become thickened and adherent if there is no effusion, and may contain tubercles or caseous masses between the layers. The symptoms and signs will be those of adherent pericardium.

Diagnosis.—Neither the symptoms nor the course of the pericarditis are sufficient to enable us to affirm the tuberculous nature of the affection. The signs of tuberculous disease in other organs and structures, especially of the serous membranes, makes the existence of a similar infection of the pericardium very probable. Hemorrhagic fluid obtained on aspiration is also strongly presumptive evidence, but even with all these conditions the pericarditis may still be due to a rheumatic or other cause. Examination of the fluid may show tubercle bacilli, but their absence from the effusion does not prove the fluid to be of non-tuberculous origin; it is often sterile, but the inoculation into animals frequently gives positive results.

Prognosis.—If the symptoms are so marked that the condition is readily recognized the outlook is not good, most cases terminating fatally early, directly from the pericardial affection, from coexisting disease in other organs, or from general tuberculosis. In some of the many cases in which the diagnosis is made postmortem, it is impossible to be certain of the duration of the pericardial disease, which may have had little or nothing to do in causing death.

In the absence of serious affection of other organs, tuberculous pericarditis usually runs a chronic course. A sharp onset followed by an acute course is exceptional. The occurrence of pericarditis in arrested or quiescent tuberculosis greatly increases the liability to renewed activity in the other lesions. Death is usually due to the general tuberculous disease or to cardiac failure. Profuse intrapericardial hemorrhage and pulmonary thrombosis have caused death in a few cases.

If adhesions of the pericardial surfaces take place, a cure results so far as the pericarditis is concerned, but cardiac failure is probably not

distant, being especially liable to occur in the tuberculous. The occurrence of tuberculous pericardial effusion in a tuberculous subject generally hastens the fatal ending.

Treatment.—The treatment of tuberculous cases is to be carried out as in other forms of pericarditis. If the fluid is abundant, it must be removed; after a time it usually reaccumulates. Caution is necessary lest the lowering of intrapericardial pressure cause rupture of fresh vessels and further hemorrhage. In a recent case, after two aspirations required at short intervals on account of the rapidity of the effusion, an injection of naphthol camphor into the pericardial cavity was followed by marked benefit.[1]

HYDROPERICARDIUM.

Hydropericardium, or *hydrops pericardii*, signifies a serous non-inflammatory transudation into the cavity of the pericardium, similar to that occurring in hydrothorax or ascites. Although the condition is analogous to pleural and peritoneal dropsical effusions, it does not occur with nearly such great frequency. It, however, probably exists, in at least a moderate degree, in all cases of marked hydrothorax.

The quantity of serum normally in the pericardium is somewhat indefinite, but there is probably not usually more than sufficient to moisten it, although the amount is doubtless subject to variation. At autopsy there are usually 5 to 10 cc. or even up to 100 cc. of clear, straw-colored, alkaline fluid, containing various salts, urea, and sometimes traces of sugar. It is said to contain more fibrin than any of the other serous transudations. Much of the transudate probably escapes at the time of death, and possibly for a time afterward.

Etiology.—The causes of hydropericardium are either local and of a mechanical nature, or general from blood changes in cachectic states and nephritis. Among the former are such as impede by pressure the pericardial circulation, such as lesions of the heart and lungs which obstruct the general venous circulation; and local affections, such as neoplasms and cicatrices in the pericardium or mediastinum, which obstruct the veins and capillaries of the pericardium. Carcinoma and tubercle of the heart and pericardium are the causes in some cases, the latter being most frequent.

Among the general causes are the cachexias of nephritis, tuberculosis, carcinoma, malaria, leukemia, etc. In these cases the pericardial dropsy is usually associated with dropsy of other serous cavities.

Symptoms.—Hydropericardium usually develops gradually without special symptoms; its occurrence is, as a rule, overshadowed by the symptoms of the cause on which the effusion depends, and by the hydrothorax with which it is nearly always associated. When the collection of fluid becomes considerable, its presence is shown by enfeeblement of the impulse and sounds of the heart, increase of the area of precordial dulness, and, it may be, fulness of the precordium. There is no friction rub. If there are no pericardial adhesions, the area of flatness on

[1] Rendu, quoted in *Traité de Médecine*, viii, 69.

percussion is modified by respiratory movements and changes of position of the patient, especially on his assuming a stooping position. In cases of marked emphysema, the area of dulness is difficult to determine, and is little affected by position. There is no fever or pain. In rapid effusion there may be some precordial distress and a feeling of thoracic constriction with dyspnœa, and disturbance of the action of the heart as in pericarditis; in these cases, some affection of the substance of the heart is probable. The effusion is usually a terminal occurrence, and rarely recognized.

Diagnosis.—A diagnosis is to be made on the basis of the signs of effusion into the pericardium without the phenomena of pericarditis, and the co-existence of fluid accumulation in the other serous cavities, of general dropsy, and of venous stasis. A consideration of the etiology is important. Often, however, it is difficult to differentiate hydropericardium and chronic pericarditis without febrile reaction occurring in nephritis or tuberculosis. The error is not of material importance.

Prognosis.—The gravity of hydropericardium is usually to be measured by that of the affection on which it depends. The debility may be so marked that the effusion, by its abundance, may itself endanger life.

Treatment.—The treatment is directed to the primary disease to which the hydropericardium is due—tuberculosis, chronic malaria, nephritis, or the state of cachexia. Diuretics, hydragogue purgatives, and diaphoretics are rarely successful. The calcium salts, as the chloride and lactate, may lessen the exudation by increasing the coagulability of the blood. When the exudate is large, relief of the symptoms may be obtained by aspiration, but it is, as a rule, only temporary, as reaccumulation is usually rapid. Aspiration is, however, rarely called for, as the patient generally suffers chiefly from the primary affection, and only in a slight degree from the hydropericardium.

HEMOPERICARDIUM.

By this is meant an effusion of blood into the cavity of the pericardium.

Etiology.—The causes of hemopericardium may be medical or surgical. Of the surgical causes, the most frequent are such traumatic injuries as penetrating and gunshot wounds; rupture of the pericardium by crushing injuries, falls from high places, or by penetration of fractured sternum or ribs, and traumatic rupture of the heart.

Among the medical causes the most frequent is spontaneous *rupture of the heart,* as a rule during violent strain; it is usually the result of degeneration of the wall of the heart, especially if a cardiac aneurism has existed. In some cases rupture of an aneurism of the coronary arteries is the source of bleeding. Rupture of an aortic aneurism into the pericardial cavity is not rare. In some cases an aneurism situated above the pericardial covering of the aorta dissects the coats down to the attachment of the aorta to the heart, and then ruptures into the cavity of the pericardium; the rupture may be small, so that the bleeding takes place slowly.

Pathology.—The quantity of blood in the pericardium varies in different cases; it depends chiefly on the size of the rupture and, consequently, on the rapidity of the bleeding. The more rapid the escape of the blood the less will be the quantity, as the result is quickly fatal; the quantity of blood may not exceed six or eight ounces. On the other hand, if the hemorrhage is slow the patient survives a relatively long time, and the volume of blood that has escaped may greatly distend the pericardium. Rolleston describes a case with a pinhole opening in the external coat of the aorta in which there were twenty-four ounces in the pericardium, and Mansell Moulin, one, with recovery, in which six pints were removed in the course of several hours.

The blood may be fluid, or coagulated wholly or only in part. In a case of Whittaker's[1] several layers of coagulated blood were stripped from the pericardium, the blood having escaped through a rupture in the heart.

Symptoms.—There is much variation in the intensity of the symptoms. If the effusion of blood is rapid, death is sudden, or at least not long delayed, and due to compression of the heart, syncope, or sudden, cerebral anemia.

If the escape of blood is slow, there are the physical signs of pericardial effusion with the general symptoms of internal hemorrhage. The onset may be with a sharp pain, or a feeling of something having given way.

Diagnosis.—The diagnosis is usually difficult, and often only correctly made *postmortem*. Following injuries, it may be evident from the nature of the cause. The diagnosis may be made if there are the signs of sudden pericardial effusion and of internal hemorrhage.

Prognosis.—The prognosis is always grave, and usually hopeless, death occurring at latest within a few days. In traumatic cases with moderate hemorrhage and an injury not necessarily fatal, recovery may take place, but cases due to rupture of the heart or of an aneurism, are almost necessarily fatal, although life may be prolonged several days. Travers reports a case of extensive traumatic rupture of the right ventricle in which death did not occur until the eleventh day.[2]

Treatment.—The treatment in rapidly fatal cases is wholly ineffective. Ordinarily it should be directed to the cause and to counteracting the effects of the loss of blood. Operation, with the object of suturing the rupture of the heart, has been successful in some traumatic cases, and should be tried in suitable ones.

PNEUMOPERICARDIUM.

Pneumopericardium consists essentially of a collection of gas in the cavity of the pericardium. In nearly all cases there is at the same time an effusion of serum (hydropneumopericardium); of pus (pyopneumopericardium); or of blood (hemopneumopericardium). The condition was recognized by the older authors, and it was very fully described by

[1] *Twentieth Century Practice of Medicine*, vol. iv, p. 50.
[2] *Lancet*, September, 1906, p. 706.

the writers of the middle of the last century. The affection is of rare occurrence. James,[1] in 1904, was able to find only 37 undoubted cases in the literature; he added 1 of his own, making a total of 38 cases.

Etiology.—Three groups of causes may give rise to the presence of gas in the pericardium; putrid decomposition of an exudate, the entrance of air through a traumatic opening, and perforation of the pericardium by an ulcerative process in a neighboring air-containing organ.

The first group presupposes the possibility of the production of gas by putrid decomposition in a closed sac. Cases with autopsy have been reported by several observers, such as Stokes, Friedreich, Duchek, Bricheteau, and others. *Postmortem* decomposition is not rare. In James' 38 collected cases there were 5 cases without perforation in the pericardium. In 1, Stokes' case, there was acute pericarditis with recovery; in the 4 fatal cases no opening was found at the autopsy.

In the second group there is a perforating wound into the pericardium by a sharp instrument or foreign body, by a gunshot wound, or by a trocar in the operation of paracentesis; in such cases the presence of the gas is due to the entrance of air either directly, or from the pleura in pneumothorax by the rupture of adhesions, or from puncture by a foreign body in the œsophagus. Perforation may be caused by a fractured rib, or a crushing injury may lacerate the lung, pleura, and pericardium, and permit air to enter from the torn lung. These were the causes in 18 of James' collection.

In the third group the ulceration may be either in an air-containing organ contiguous to the pericardium, or in some structure the seat of a purulent inflammation. The most frequent processes that occasion such an accident are: an ulcerating cavity in the lung, pyopneumothorax, cancer of the œsophagus, gastric ulcer perforating the diaphragm, and a subdiaphragmatic abscess perforating both pericardium and stomach, or, possibly, the intestine. There were 15 cases due to these causes in James' collection.

Pericarditis is very frequently associated with pneumopericardium, and as the germs are usually pyogenic the inflammation is nearly always purulent. Mueller is said to have met with a case of serous exudate, and Stokes reports a case of acute pericarditis followed by hydropneumopericardium with cure.

In 7 cases, air entered from the œsophagus; in 3 of these from perforating cancerous ulceration, 1 from unspecified ulceration, and in the remaining 3 from traumatism. In 8 cases air entered through a penetrating wound from without; in 4 from a softened tuberculous focus in the lung or in a lymph gland; in 7 from crushing injury causing fracture of the ribs or sternum, and laceration of the pericardium; in 2 from an abdominal abscess, 1 of the liver, and 1 of the appendix. In 2 it was from gastric ulcer; in 1 from pneumothorax; in 1 from pneumonia with gangrene of the lung, perforating the pleura and later the pericardium. In 1 case, some disease of the lung perforated into the œsophagus and later into the pericardium.

[1] W. B. James, Pneumopericardium, *American Medicine*, July 2, 1904, p. 23.

Pathology.—The essential condition consists in an accumulation of gas in the upper part of the pericardial cavity, a collection of liquid in the lower part, and the existence of a pericarditis, usually intense, secondary to a rupture of the serous membrane. The composition of the gas is variable; it is usually fetid from putrid decomposition of the purulent exudate. The pericardium is usually distended, and on puncture the gas escapes with a hissing sound.

Symptoms.—The symptoms vary greatly according to the cause and the nature of onset. If the condition develops gradually, the symptoms will be those of a mild pericarditis until the distension of the sac becomes great, and causes symptoms of pressure on neighboring organs and functional disturbances of the heart. But in the traumatic forms, the entrance of air is sudden and marked by the brusque appearance of subjective phenomena, such as sudden retrosternal pain of a burning character, precordial oppression, palpitation, dyspnœa, and of thready pulse, cyanosis, etc. There may be recurrent syncopal attacks. The symptoms closely resemble those presented by the various forms of pneumothorax. Dysphagia from pressure on the œsophagus has been reported (Eisenlohr).

The *physical signs* are, in most cases, strikingly characteristic. This is shown by the frequency with which the cases were recognized by all observers, nearly all of whom were meeting with the condition for the first time. In only 6 of the 38 cases was the condition not recognized before autopsy (James). On inspection, the precordial region is prominent, at least in the intercostal spaces, and the cardiac impulse is not visible, but may return with normal force and become visible if the patient assumes the prone position. The percussion sound is tympanitic, of a metallic character, and disappears as the patient assumes the prone position.

As the effusion increases, the lower part of the precordial area becomes flat, the upper remaining tympanitic; with change of position of the patient there is a corresponding change in the relationship of the areas of tympany and flatness. Systole may bring the heart against the chest wall and the note will then be dull. Cracked-pot sounds may be present even without a communication between the pericardium and a bronchus (Stokes). An *x*-ray examination should give a characteristic picture.

The most characteristic sign of the presence of fluid and gas is the churning, splashing sounds audible over the precordium and synchronous with the heart's action. It was noted in one-half of James' collection, under a variety of descriptions, as bruit de Moulin, de roue hydraulique, metallic gurgle, etc. It is of the same character as the succussion sound produced by shaking a patient with hydropneumothorax. Metallic tinkling sounds were heard in 24 cases, also synchronous with the movements of the heart, and usually blended with the churning, splashing sound. The tinkling may be audible at a distance from the patient, who may himself hear it, and be conscious of the tumultuous action in his chest. As the liquid exudate becomes abundant the cardiac sounds are weakened and may disappear; more often they are masked by the various pathological sounds. Pericardial friction sounds of variable

intensity are frequently heard; in some cases there is a fine crepitation—due to emphysema of the cellular tissue in front of the pericardium.

Diagnosis.—This is usually easy on account of the marked and characteristic signs. The condition might be simulated by left pneumothorax, especially if confined to the outer part of the pleura, and by a large pulmonary cavity in contact with the pericardium. In such conditions the normal outline of the heart, its impulse, and the arrest of the various churning, metallic, and other sounds on suspending respiration would be diagnostic.

Gaseous distension of the stomach sometimes causes metallic heart sounds, but confusion with pneumopericardium should not occur if the existence of the normal area of heart dulness, the cardiac impulse, and the absence of material functional troubles and disturbances of the heart are taken into consideration. The passage of a stomach tube would give vent to the gas and definitely settle the diagnosis.

Emphysema of the tissue in front of the pericardium from traumatism presents some of the signs of pneumopericardium.

Prognosis.—Of the 38 cases collected by James, 26 terminated fatally, and 11 in recovery. In 8 of the 26 cases nearly all the causes of the pneumopericardium were in themselves fatal; they were such as cancerous and other perforations of the œsophagus, gastric ulcer and hepatic abscess perforating the diaphgram, and tuberculous ulceration and gangrene of the lung opening into the pleura and later into the pericardium. The large number of recoveries shows that the heart is remarkably tolerant of pericardial disease, that is, so long as its own substance is not involved. Much may depend on the suddenness of the distension of the pericardium with gas, as shock will be induced in the cases of sudden development, and add greatly to the danger.

Treatment.—In traumatic cases, the opening should be closed at once by an antiseptic dressing; this is the most important part of the treatment. If an abundant exudate occurs, with the signs of a distended pericardium, and threatening cardiac collapse from compression, evacuation of the pericardial contents becomes necessary. If the exudate is purulent and putrid, the original opening should be enlarged to give free discharge to the pericardial contents. Some advise irrigation with warm antiseptic solution. In fistulous cases the treatment is simply palliative.

NEOPLASMS OF THE PERICARDIUM.

The various neoplasms of the pericardium are malignant, as *carcinoma* and *sarcoma*, and non-malignant, as fibroma, enchondroma, free bodies, and hydatids.

Malignant Neoplasms.—Cancer and sarcoma may be *primary* or *secondary*.

Primary cancer is very rare, even its occurrence is disputed. Of the cases reported it is not clear how many are cancer and how many are sarcoma. Sir W. Broadbent reported a case of sarcoma of the peri-

cardium in 1882,[1] and Williams and Miller[2] a case of primary sarcoma in a girl, aged thirteen years. Broadbent's case was in a stout, florid man, aged twenty-three years, who complained of some discomfort in the lower part of the thorax. For two months he had had pain in the shoulders and down the arms, with dyspnœa on exertion. After the onset of the dyspnœa there were signs of fluid in the left pleura, also in the pericardium. Three weeks later there was no fluid in the pleura, but the pericardium was apparently distended and the dyspnœa increased, He was tapped, but no fluid was obtained; the trocar impinged upon a firm fixed mass. He died three days later. At the autopsy, the pericardium was found one-half inch thick at the base, the thickness increasing upward and being one and one-half inches at the great vessels. On examination it proved to be sarcomatous.

Secondary growths are scarcely more frequent. In 477 cases of cancer in various parts, in only 7 was the pericardium affected (Williglk). Kobler met with cancer 6 times in 9118 autopsies. It may be secondary to cancer of the heart or of some neighboring part, as the mediastinum, the bronchial glands, the pleura, lung, or œsophagus. It is sometimes involved in cases of generalized metastatic nodules secondary to cancer of distant organs. In it are reproduced the anatomical characters of the original disease; this is true of sarcomatous growths also. They always give rise to pericarditis with more or less effusion, which may be serous, oftener hemorrhagic, and sometimes purulent or even putrid. In some cases the invasion occurs as a diffuse infiltration, affecting more or less extensively the serous membranes and subjacent tissues; in others, the disease occurs in the form of distinct growths.

Symptoms.—The symptoms are those of mild or chronic pericarditis with the general, grave condition usually occurring in malignant affections. The subclavicular glands may be involved and render the diagnosis quite clear. If aspiration is rendered necessary by the abundance of the effusion, a hemorrhagic fluid is usually obtained; it is, however, occasionally purulent and even putrid. There may be the signs of primary or secondary carcinoma.

Diagnosis.—This is easy if malignant disease can be demonstrated in other parts of the body. In the absence of such growths the diagnosis may be impossible. The possibility of a mediastinal tumor being malignant should be borne in mind; it may simulate pericardial effusion.

Prognosis.—The prognosis is necessarily fatal, and the duration brief.

Treatment.—This is wholly symptomatic, the objects being to relieve distress and maintain strength. If the effusion is abundant, aspiration will be necessary; it is questionable if free drainage will be desirable, even if the exudate is purulent or even putrid.

Various Neoplasms.—Occasional reference occurs in the literature to non-malignant neoplasms in the pericardium. Bouchard reported a case of polypus in a child aged four years. Free bodies in the cavity of the pericardium have been found; they owe their origin probably to

[1] *Transactions of the Pathological Society of London*, vol. xxxiii, p. 78.
[2] *New York Medical Journal*, April 14, 1900.

polypi or free fringes. They may consist of soft tissue, or of firm, fibroid structure, and are occasionally calcareous (cardioliths).

Fibroid tumors and *lymphomas* of the pericardium have been reported, and one case of cystic enchondroma has been met with.

Bouchard has described fringes resembling those met with at times in the knee and other joints; they are of occasional occurrence. They may be pedunculated, or even become free, forming soft, foreign masses. Foreign bodies may also arise from a coagulum of fibrin, or from inspissated pus in which lime salts have become deposited.

Hydatids.—Hydatids of the pericardium are very rare. The late Davies Thomas, of Australia, found the record of only two cases. Cases have been reported by Barlow, Enos and Rapp, Chadzynski, Bernheim, and MacDonald. In Chadzynski's case the cyst was very large and ruptured into the pericardial cavity. Hydatid cysts of the pericardium present no symptoms of special significance. As a rule, hydatids coexist elsewhere and may guide to a correct diagnosis.

SYPHILIS OF THE PERICARDIUM.

The *pericardium* is so rarely the seat of syphilitic infection, and the few cases in which infection occurs shows such indefinite, if any, symptoms, that the subject is of academic interest rather than one of practical medicine. Ricord, in 1851, was the first to describe the disease; in his case there was some fibrinous exudate on the pericardium. Virchow, in 1861, described the second case recorded; in this case there was adhesion of the pericardium. In 1897, Phillips[1] collected 25 cases of syphilis of the heart, and in 5 of these the pericardium was involved. Most works on diseases of the heart make no reference to the disease, and, of those that do, few give it more than a passing notice. Gibson[2] gives a fairly full description, and Babcock[3] discusses the subject at even greater length.

Pathology.—An adequate explanation for the relative immunity of the pericardium to syphilitic infection may be found in its slight vascularity. The point of syphilitic infection, in all organs and tissues, appears to be the wall of the bloodvessels, probably by way of the lymphatics. In proportion to its vascular supply, syphilitic disease probably affects the pericardium quite as frequently as it does the meninges of the brain. In nearly all the cases published the pericardial lesion has occurred in association with syphilitic disease of the subjacent muscular tissue. As a rule, only the visceral pericardium is affected and the lesion is usually a circumscribed inflammation, rarely a gummatous deposit. Beneath the inflammatory areas is usually found some fibrosis of the muscular tissue or a gumma imbedded in the wall of the heart. The parietal pericardium in contact with the affected visceral layer may become infected. The vessels of the affected pericardium are hyperemic,

[1] *Lancet*, 1897, vol. i, p. 223.
[2] *Diseases of the Heart and Aorta*, 1898, p. 381.
[3] *Diseases of the Heart and Arterial System*, 1903, p. 138.

but as the new cicatricial tissue is organized and contracts, they become obliterated and a white scar results. Fluid exudate appears to be rare, so that its presence, whether serofibrinous or hemorrhagic, is indicative of tuberculous rather than syphilitic disease.

Gumma of the pericardium is very rare. Marcek[1] was able to find only three undoubted cases described; since then no fresh cases seem to have been reported.

Symptoms.—Of the pericardial lesion itself there are probably no symptoms; the disease of the myocardium, with which it always appears to be associated, can, no doubt, cause all the symptoms that may be present during the course of the pericardial affection.

Diagnosis.—A pericardial lesion may be suspected in a syphilitic case that shows signs of a cardiac affection, but its existence can neither be demonstrated nor excluded. In rare cases, possibly, there may be a friction rub.

Prognosis.—Syphilis of the pericardium, of itself, can scarcely have any influence on the duration of life, and probably rarely causes any disturbances of comfort.

Treatment.—In so far as the pericardial lesion is concerned, the question of treatment is one of academic interest. In a suspected case, mercury and the iodides should be employed freely. Salvarsan should be given unless contraindicated by grave changes in the heart.

ABSENCE OR DEFECT OF THE PERICARDIUM.

Complete absence of the pericardium is rare; it is usual in cases of serious anomaly, such as ectocardia, etc. Partial defect is more frequent, the pericardium usually taking the form of a falciform fold projecting upward from the diaphragm and forming an incomplete pericardial sac. Bristowe described a specimen which consisted of a rudiment of the pericardium at the upper and right side of the heart. In one case of incomplete pericardium, death resulted from dislocation of the heart during a severe attack of vomiting.

[1] *Archives f. Dermatologie u. Syphilographie*, Band xxv, S. 279.

CHAPTER III.

THE RATE AND MECHANISM OF THE HEART BEAT.

By THOMAS LEWIS, M.D., F.R.C.P.

Historical and Introductory.—Our latest conceptions of heart disease have originated from the physiological work of the late seventies and eighties. Although the heart beat had been regarded by Haller as a peristaltic wave of contraction, passing from the venous inlet to the arterial outlet, yet this view found no general acceptation until after the experiments of Gaskell, MacWilliam, Engelmann and others.

It has been shown that the beat of the ventricle is initiated by the contraction of the auricle and that in the cold-blooded heart, where the sinus and auricle are clearly delimited, the auricle receives its impulse to contract from the sinus region. The work upon the frog and tortoise heart was quickly followed by similar observations upon the mammalian heart, and attention became focussed upon the anatomy of those regions of the mammalian heart where auricle joins ventricle, and where sinus remains were supposed to exist.

Knowledge progressed to the discovery of two clearly differentiated structures in the mammalian heart; the auriculoventricular conducting system, which forms the functional union between auricles and ventricles, and the sino-auricular node, lying near the mouth of the superior vena cava; the heart beat is now known to arise in this node. The modern conception of the heart beat is based upon extensive study of the anatomy, physiology, and morphology of that organ, and a certain familiarity with these studies is essential to the correct understanding of normal and perverted heart mechanism. The controversy between those who have advocated the myogenic or the neurogenic origin and transmission of the contraction wave has had a conspicuous influence upon the trend of observation. These rival hypotheses have prompted the discovery of many new facts; nevertheless, it still remains uncertain which is permanently to hold the field, and the time is not yet ripe when one or other should be allowed materially to sway our conceptions of pathological processes. More especially is this the case while the myogenic doctrine, being ascendant, has become associated with a doctrine of manifold function of heart muscle.

The strict separation of the five cardiac functions — rhythmicity, contractibility, excitability, conductivity, and tonicity—is one which is jealously guarded by many writers, and more especially by those who have followed in the footsteps of Engelmann. That the heart musculature —and by the term "musculature" I mean the cardiac muscle in full functional connection with its nerves—has these attributes is clear;

but that certain of the functions are special attributes of particular regions of the heart, a fact brought into prominence by Gaskell's writings, has not received sufficient emphasis by many later workers. The tendency of clinicians to class disorders of the heart beat according to perversions of one or other of these so-called functions, I regard as unfortunate.

If the controlling cardiac impulses are initiated in an abnormal manner, the derangement is to be regarded, not necessarily as a disturbance of the function of rhythmicity, but as a disturbance of the functions of the special tissue lying in the region of the superior vena cava, and known as the sino-auricular node. Similarly, disturbances in the transmission of the contraction wave in its progress from auricle to ventricle must be regarded, not as a disturbance of conductivity, but rather as a derangement of those special tissues forming the paths through which the contraction wave flows. A clearer conception may be formed if the disorders subsequently to be spoken of as auriculoventricular heart-block are instanced.

To describe dissociation between auricles and ventricles as a disturbance of conductivity, using this word in its special sense, is misleading. The disturbance is often brought about by complete transection of the tissues uniting the two chambers. Under this circumstance we clearly deal not with disordered function, but with structural damage. Again, the classification of premature contractions or extrasystoles as disturbances of excitability is not warranted by our knowledge of the former or by our definition of the latter. Excitability of any region of the heart is defined as its property of responding to artificial excitations, mechanical, chemical or electrical. We have no evidence that the excitability is raised in those hearts which give rise to the new beats; we have some evidence to the contrary. Whatever may be the value of separating and isolating the normal cardiac functions, the division forms but an insecure foundation in classifying disorders of the heart beat at the present time. The classification adopted in the present chapter is based upon the simple facts at our disposal rather than upon a hypothesis which may prove unfounded.

As it is to experiments upon animals that we owe our knowledge of the normal heart mechanism, so it is mainly to similar experiments that we look for our earliest acquaintanceship with disordered mechanism. To the names already given those of Erlanger, of Hering and many others might be added. But the knowledge of perverted action in animals could never have been applied to the human subject but for further enterprise. The correlation of experimental and pathological facts has been facilitated by a number of workers. Wenckebach and Cushny have the credit of first comparing the clinical irregularities of the ventricle with those induced experimentally; Mackenzie and Einthoven by elaborating special graphic methods have given us ready means of recording the movements of the different chambers of the heart.

The sino-auricular node (of Keith and Flack) in the human heart is a small neuromuscular organ lying in the upper reaches of the *sulcus terminalis*, near the junction of the superior vena cava to the right auricle. The muscle of this important structure consists of fine spindle-

shaped interlacing fibres, imbedded in a dense meshwork of connective tissue and richly supplied by nerve elements (especially, on the inhibitory side, by fibres of the right vagus). In it the normal heart beat originates, spreading to both auricles and to the junctional tissues at the auriculo-ventricular ring.

The auriculoventricular junctional system has its origin in the septum of the auricles where small muscle fibres collect fanwise to a centre and eventually interlace to form a second node, the auriculoventricular node (of Tawara). This node has a similar structure to that previously described and is also richly endowed with nerves. It is continued as the auriculoventricular bundle (the bundle of Kent and His), which after piercing the auriculoventricular ring and approaching the upper borders of the membranaceous septum breaks into two main branches, right and left, respectively. The main branches course along the septal walls of the corresponding ventricles and, breaking into a complex arborization (the network of Purkinje), are distributed to the ventricular muscle. This system possesses the function of carrying and distributing those impulses which descend from auricle to ventricle. Thus the rhythmic impulses arise in the sino-auricular node under the governance of the great heart nerves; they awaken contractions in the auricles and these in their turn send messengers to the ventricles, again under the governance of the great heart nerves, and through the medium of the special structures described. Such is the simple plan of the rhythmic and coördinate heart beat as we know it. But the junctional tissues between auricle and ventricle subserve at least one other function: they act as subsidiary centres, from which, in the time of need, rhythmic impulses are elaborated and sent to the ventricles. Like the sino-auricular node they are specially endowed with the power of awakening heart beats, and this property is called into play when the union between auricle and ventricle is disturbed.

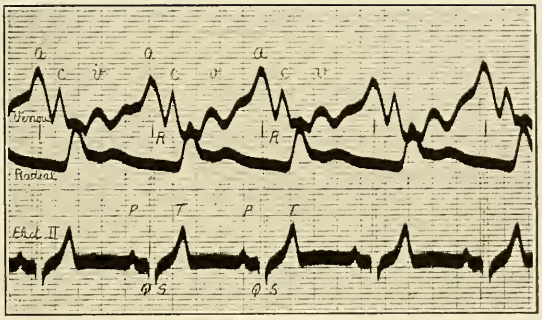
Polygraphy is a mechanical method of obtaining separate and simultaneous records of the auricular and ventricular contractions. As ordinarily practised, a curve (Plate I, Fig. 1) is taken from a large artery, another from the veins at the root of the neck; the first signals the movements of the left ventricle (and, as the two ventricles beat together, of the right ventricle also), the second signals the movements of the right auricle (and, as the two auricles beat together, of the left auricle, also). When the normal sequence of contraction is disturbed the disturbance is analyzed by identifying the instants of contraction in the two main subdivisions of the heart (auricle and ventricle) relative to each other. It is essentially a bed-side method.

Electrocardiography is a method practised with similar objects in view, but it is of far greater accuracy and takes the analysis further. Besides recording the separate contractions in auricle and ventricle (Plate I, Fig. 1), it speaks definitely of the *direction* of contraction in the muscle of the separate chambers.

As an accompaniment of systole in auricles or in ventricles, electric energy is developed in the heart, and is diffused throughout the whole body. It is tested in the limbs, which are connected to a suitable and

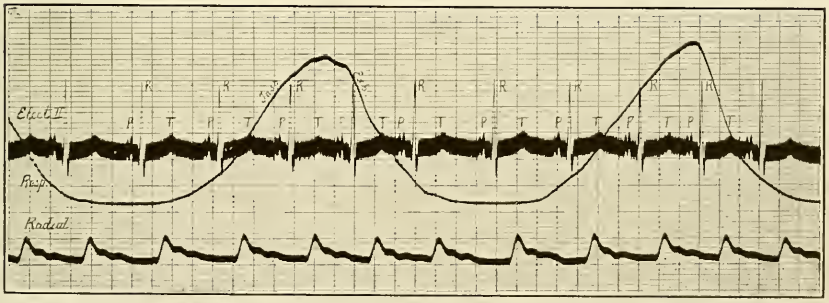
PLATE I

FIG. 1



Simultaneous curves taken by a photographic method. × ⅔. Venous, arterial, and electrocardiographic curves are shown. The vertical lines mark fifths of a second in these and subsequent figures. The horizontal lines are at millimeter distances, and the electrocardiograms are so standardized that one millivolt corresponds to 10 millimeters on the scale. Any vertical line cuts the three tracings at the same instant in time. In the case of the two mechanical curves an allowance of 0.016 second must be made for time lost in the instrument. The same remarks apply to subsequent and similar figures. The venous curve consists of *a*, *c*, and *v* waves; the wave *c* occurs about one-tenth of a second before the radial upstroke and is coincident with arterial pulsation in the neck. It marks the onset of ventricular systole in the venous curve. Preceding it is a wave *a* falling in presystole and resulting from the contraction of the auricle. Lastly, the summit *v* occurs opposite the bottom of the dicrotic notch in the arterial curve, the wave marks the end of ventricular systole. In the electrocardiogram, *P* corresponds to systole in the auricle; the deflections *Q*, *R*, *S*, and *T* correspond to ventricular systole. The auricular and ventricular events in the electrocardiogram precede similar events in the jugular curves by a little more than one-tenth second. This difference is due to (1) the appearance of the electric effects very slightly before contraction in the muscle (about 0.02 second), (2) delay in transmission of the venous waves from the auricle to the neck (about 0.10 second), and (3) delay in the transmission of venous waves through the recording instrument (about 0.016 second).

FIG. 2



Simultaneous electric, respiratory curves and arterial tracing. × ⅔. The irregularity is of sinus origin and is coincident with the phases of respiration as shown on the curve. There is a quickening of the heart rate and pulse rate during the phase of lowered intrathoracic pressure, and a retardation during the phase of raised intrathoracic pressure.

highly sensitive galvanometer. With each normal heart cycle the auricles yield currents, which change in amount and direction; so, too, in the case of the ventricle; these currents flow through the instrument and are recorded by it. Each subdivision of the heart gives its own curve, a curve characteristic of normal contraction; for the shape of the curve is controlled by the direction of the excitation wave in the muscle giving birth to it. Suitable experimentation allows the direction of contraction, normal or abnormal, to be identified.

Pathological Types of Disordered Mechanism.—The chief types of disordered heart mechanism may be described under the headings which succeed. They are:

1. Disturbances of impulse production.
2. Heart-block.
3. Premature contractions or extrasystoles.
4. Simple paroxysmal tachycardia.
5. Auricular flutter.
6. Auricular fibrillation.
7. Alternation.

1. **Disturbances of Impulse Production.**—The disturbances of heart-action which fall under this heading are broadly three in number, namely, increase of rate (simple tachycardia), decrease of rate (simple bradycardia) and irregular action ("sinus irregularity"). In each and all of these states the sequential action of the separate chambers is undisturbed; the impulses creating contractions all arise at the natural pace-maker or sino-auricular node, and all the heart chambers are equally and successively involved in the disturbance.

Simple Tachycardia, or Rapid Heart Action.—Simple tachycardia may be produced experimentally in one of three chief ways, (*a*) by altering the innervation, for example by section of the vagi, by administration of atropin, or by stimulation of the sympathetics; (*b*) by altering the chemical environment of the pace-maker, for example by acidifying the blood or by the injection of adrenalin, salts of sodium, etc.; (*c*) by altering the physical environment, a notable example of which is the reaction to increased temperature.

In the human subject, simple tachycardia is seen in a variety of conditions and the exact manner of production is often unknown. The heart rate may be persistently far above the average (to 100) as a physiological variation in the healthy subject. The rate is much faster in children than in adults, it increases with exercise (to 180), with mental effort or excitement, and with the application of heat to the body. It is increased by fever and in all acute febrile diseases; though to a lesser extent in those which affect the central nervous system and in typhoid fever. Simple tachycardia is prominent after hemorrhage and shock. It follows lesions of the vagi, especially the right nerve, and is a usual and special feature in exophthalmic goitre. Simple tachycardia is often associated with local infections, whether fever is present or not, notably in pulmonary tuberculosis, pericarditis, etc. It occurs in intoxications, especially in belladonna poisoning and in chronic alcoholism. A high ventricular rate is frequent in mitral stenosis, in aortic

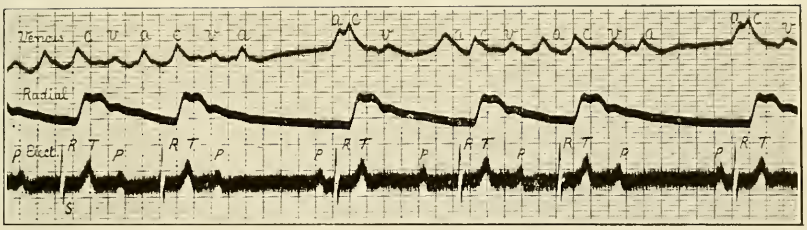
regurgitation, and in renal disease associated with Cheyne-Stokes breathing (80 to 100). As a temporary disorder, simple tachycardia is often encountered in those who present signs of nervous irritability, giving rise oftentimes to attacks of *palpitation;* overreaction of the heart rate to simple causes is seen in these subjects, in those who are convalescing from acute illnesses, and in those who are the subjects of chronic infection or whose health is generally impaired.

The Irritable Heart of Soldiers and So-called Heart Strain.—The irritable heart of soldiers is a term used originally by Da Costa in describing a condition met with in campaigners of the American Civil War. A persistent tachycardia (90 to 120 or more) was one of the symptoms discovered in a number of soldiers. The patients, often young and raw recruits, submitted to the rigors of a strenuous campaign, underfed, exposed, sufferers from fever, diarrhœa, scurvy and wounds, developed symptoms of palpitation, dizziness, precordial pains and dyspnœa. An abrupt, jerky, and extended impulse, increase of heart rate with or without slight or gross irregularity, paroxysms of acceleration, usually in the absence of murmurs and signs of hypertrophy, constituted the chief signs. The majority progressed to recovery. The group is not a distinct one and in this respect, as well as in others, bears a close resemblance to that of "heart strain" so-called. The pathology of these conditions cannot be held to be special, nor can many of the patients be grouped as subjects of primary cardiac disease. Some it is true are described as presenting distinct signs of myocardial involvement, those especially in whom paroxysms of tachycardia and gross irregularity were observed; but such patients belong to groups which we shall consider hereafter, and tachycardia of these types should be rigidly separated from those examples of simple acceleration which are our special consideration in this section. The terms "irritable heart" and "strained heart" are terms which have been used in a comprehensive and loose fashion to cover ailments, the natures of which were imperfectly understood. There is a common misconception that dilatation of the heart produces tachycardia. Direct experiment shows that this is not the case. When dilatation and tachycardia are associated, the dilatation is secondary to the tachycardia or both are due to common or different causes.

Simple bradycardia or slow heart action may be obtained experimentally (*a*) by altering the innervation, for example by continued stimulation of the vagi, electrically or by the administration of morphia; (*b*) by altering the chemical environment of the pace-maker, notably by the injection of potassium salts or by prolonged asphyxia; (*c*) by altering the physical environment of the pace-maker, notably by the application of cold. Slowing of the whole heart is associated with a variety of conditions in the human subject. Although the rate of 72 per minute has long been accepted as an average rate in the normal subject, lower rates (55 to 60 to 65) are not infrequently seen in perfectly healthy individuals. The heart rate is often slower during the last half of the second decade and is frequently below the average in athletes at rest. I have seen a notable example in a perfectly healthy athlete, whose heart rate while he was quiescent was habitually between 30 and 40 per minute.

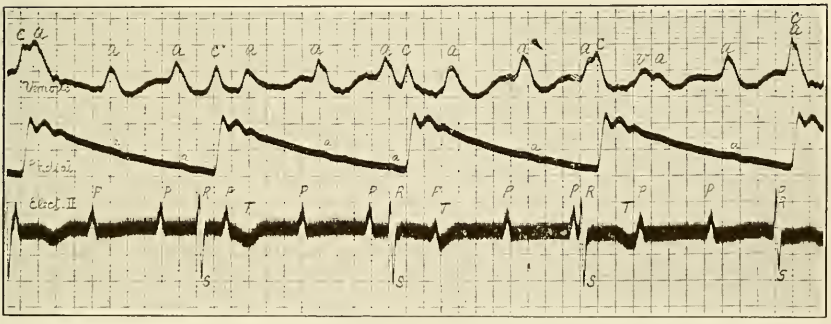
PLATE II

FIG. 1



Simultaneous arterial and electrocardiographic curves, showing partial heart-block. × ⅔. The *a-c* interval and the *P-R* interval are prolonged to double their normal values, except at the ends of the longest pauses. On two occasions the ventricle fails to respond to the auricular contraction and an *a* wave in the venous curve, a *P* summit in the electrocardiogram, appears in an isolated fashion. The heart-block is responsible for the intermittence occurring at regular intervals in the pulse.

FIG. 2



Simultaneous curves showing complete heart-block, or dissociation of auricular and ventricular contractions. × ⅔ The rate of the radial pulse is 27 per minute; the rate of the ventricle is the same; the rate of the auricle is 75 per minute. The relation of auricular and ventricular systoles is especially well shown in the electrocardiogram. The auricular summits *P* occur at regular intervals throughout the whole curve, so do the deflections corresponding to the ventricles (*R*, *S*, and *T*). Opposite and a little later than each ventricular complex (*R*, *S*, and *T*) is a solitary radial pulsation; opposite and a little later than each *P* summit is a wave *a* in the jugular curve, and a minute *a* wave upon the radial curve. Where *a* and *c* fall together, larger waves occur. Note the accurate manner in which auricular and ventricular deflections superimpose when they fall synchronously. In the last cycle, *P* falls upon *R* and *S*; *R* is consequently raised and *S* is less deep.

The rate decreases in adults with advancing years; it may be peculiarly slow during the puerperium. It decreases subsequent to exercise, is often slow in fatigue, and may be retarded by exposure to cold. The heart rate is often slow during convalescence from acute illnesses. Retardation of the heart may be associated with gross cerebral lesions, more especially tumor, apoplexy and meningitis. It is seen in myxœdema, and is said to occur in the epileptic, in melancholia and hypochondriasis. Jaundice, diabetes and certain forms of uremia (especially if the blood pressure is raised) are often accompanied by it. It is said to occur with notable frequency in disease of the alimentary and genito-urinary tracts. The heart rate is often slow in aortic stenosis.

Sinus irregularities may be defined as irregularities of the heart which are produced by interferences with the rhythmic impulses at the seat of their discharge, namely the natural pace-maker; they are generally due to changes in vagal tone. Sinus irregularities affect all the heart chambers equally, and are of several types. We may consider the three most important:

(*a*) *Respiratory Irregularity.*—In dogs, a waxing of heart rate with inspiration and a waning with expiration are prominent and normal phenomena. The same irregularity is often encountered in perfectly healthy children, though the degree in which the heart rate changes is less; in young adults the same periodic change of rate happens when the breathing is deepened (Plate I, Fig. 2).

(*b*) *A sinus irregularity independent of respiration* is met with in some young subjects in health, and also occurs as does the respiratory irregularity when the pulse is slow after exercise and during convalescence from acute illnesses. Both may be produced by digitalis administration. The sinus irregularity is not necessarily periodic, but becomes so if the breathing is deepened and the periods are then synchronous with the acts of breathing.

(*c*) *Standstill of the Heart.*—Exceptionally, syncopal attacks are the result of cessation of the whole heart beat. The standstill results from vagal discharges and is in every way comparable to the standstill which results when the right vagus is excited experimentally. The clearest clinical instance of this kind has been described by Laslett; others have been recorded by Mackenzie and Wenckebach; Neuberger and Edinger's case, in which an aneurism pressed upon the medulla, probably belongs to the same group. Syncopal attacks may be produced in the healthy subject, as Czermak first demonstrated, by pressing upon the vagus in the neck.

2. **Heart-block.**—Auriculoventricular heart-block may be defined as an abnormal heart mechanism in which there is a delay in the response, or an absence of response, of the ventricle to auricular impulses. Normally the ventricle contracts about a fifth of a second after the auricle. Heart-block occurs in two forms; either it is partial or it is complete. If *partial*, then the block may consist (1) simply of a prolongation of the intervals between corresponding auricular and ventricular contractions; (2) of dropped beats (Plate II, Fig. 1), the ventricle failing to respond to an auricular stimulus from time to time; (3) of a reduction of ventricular

rate to one-half, one-third or one-quarter, the auricular rate being maintained. In *complete* block (Plate II, Fig. 2) the auricles and ventricles beat at independent rates, the ventricle elaborating its own impulses (from the junctional tissues) at a rate of 30 or more beats per minute.

Heart-block may be produced experimentally in one of three ways. (*a*) By direct interference with the auriculoventricular bundle, which conducts the impulses to the ventricle. Thus pressure upon this tract will, according to its degree, produce varying grades of block (Erlanger). Firm compression or section of the bundle dissociates the contractions of auricle and ventricle and produces complete block. (*b*) By stimulation of the vagus, especially the left nerve. (*c*) By intoxication; for example, by asphyxiation, by the injection of digitalis or an allied drug, or large doses of adrenalin or diphtheria toxin.

In the human subject heart-block is seen at all ages from birth to old age. It usually results from a demonstrable lesion in the course of the auriculoventricular bundle. The hearts from over 70 subjects of this malady have received careful examination; very few cases have been recorded in which lesions could not be found in this situation. The lesions appear near the central fibrous body of the heart and in the membranaceous septum; the most frequent being localized gummata or less clearly defined infiltrations or scarrings of syphilitic origin; or simple fibrosis, combined or uncombined with calcareous deposits. An ulcer invading the tract, an endothelioma starting in it, tumors (fibromata, etc.) or necrosis involving this bundle have also been described among other lesions. In acute cases lymphocytic deposits are the rule. Of the infective diseases, rheumatic fever is especially concerned in the production of heart-block; it is also seen in diphtheria, influenza, pneumonia, and typhoid fever. In my own series of 38 observed cases, 4 gave a history of syphilis and 12 a history of rheumatic fever; the preponderance of the latter is due to the relative frequence of partial heart-block as an acute or subacute affection.

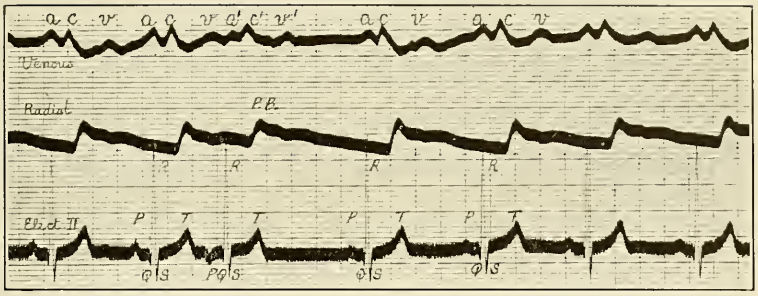
Heart-block may also result in the human subject, temporarily at all events, from vagal influences; it may be produced by deliberate pressure upon the vagus in the neck. Heart-block when present has been relieved by the administration of atropin and in a few cases lesions of the vagus have been described, though no such case is beyond criticism. Chronic heart-block is probably never to be attributed solely to this cause.

Heart-block also occurs in susceptible subjects during the administration of digitalis, strophanthus and squill.

3. **Premature Contractions or Extrasystoles.**—Premature contractions are to be defined as responses of the heart to new and isolated impulses formed in the musculature; they are contractions which occur before the anticipated time and which consequently disturb the rhythmic movements of the heart. Premature contractions are of two chief kinds: some arise in the ventricle, others in the auricle. Arising in the auricle, they spring, not from the pace-maker, but as a rule from some extraneous or ectopic point. The premature auricular contraction is followed by a similar beat in the ventricle (Plate III, Fig 1), which, therefore repeats the auricular irregularity. The premature ventricular contraction (Plate

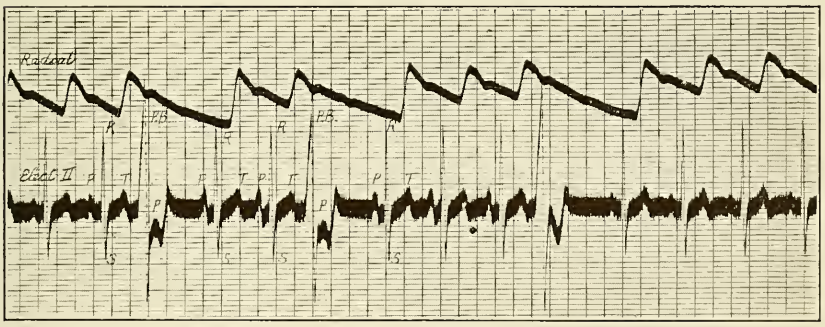
PLATE III

FIG. 1



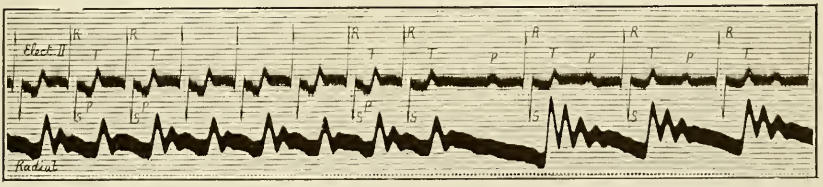
Simultaneous curves illustrating a premature contraction or extrasystole of auricular origin. × ⅔. The normal rhythm is interrupted by an early beat which shows itself in each curve. The arterial curve shows the early ventricular beat; in the venous curve this early ventricular beat is accompanied by c' and v' waves, and c' is preceded by a wave a', corresponding to the premature auricle. The same events are shown in the electrocardiogram, where the early beat is represented by defections, P, Q, R, S, and T. The beat arises in some ectopic auricular focus, it spreads in an abnormal manner through the auricle, and consequently gives an abnormal P deflection. It spreads from the auricle in normal fashion to the ventricle and consequently gives normal ventricular deflections, Q, R, S, and T.

FIG. 2



Simultaneous radial and electrocardiographic curves showing premature contractions or extrasystoles of ventricular origin. × ⅔. The normal beats of the heart are accompanied by P, Q, R, S, and T deflections. After each second or third normal heart beat, a premature contraction arises in the ventricle; it courses through the ventricle in an abnormal direction and the corresponding ventricular curve in the electrocardiogram is therefore highly abnormal. Because of its prematurity it is weak and gives rise to no arterial pulse beat. The pulse consequently intermits.

FIG. 3



Electrocardiogram and arterial pulse curve showing the termination of a paroxysm of tachycardia. × ⅔. In the radial curve the rapid heart action is terminated by a long pause and the normal and slower heart action is then resumed. The ventricular electrocardiograms of the fast and slow period are exactly alike, showing that during the paroxysm the heart beats arose, as in the normal period, from a supra-ventricular focus. The auricular contractions are to be made out in the electrocardiogram; during the slow period they are of normal outline but the P-R interval is increased; during the paroxysm the auricular contraction consists of an inverted deflection which notches the commencement of T in each cycle, except the last. Note the alternation of the pulse during the paroxysm. The time marker in this curve is in thirtieths of a second.

III, Fig 2), on the other hand, does not disturb the sequence of auricular contractions; the disturbance is confined to the ventricle. Premature beats very frequently cause grouped beating of the ventricle, regular alternate beats being premature, or a premature beat occurring after a fixed number of normal cycles (two, three, four, or more). When they fall early in diastole they may not raise the aortic valves, and the pulse rate is then slower than the ventricular rate. Not uncommonly the pulse rate may be halved in this manner.

Experimentally they may be induced by applying isolated shocks (electrical or mechanical) to the muscle, by suddenly raising arterial pressure (Hering) or by the administration of poisons (notably chloroform in small doses, adrenalin, digitalis, chlorides of barium and calcium, aconitin, nicotin, etc.). They may be caused by producing anemia of the heart, when for instance the muscle is robbed of its blood supply by obstruction of the caval veins or branches of the coronary arteries. If a predisposition to extrasystole formation is awakened, then stimulation of the sympathetic nerves enhances the tendency.

In the human subject extrasystoles are seen in early life as accompaniments of infectious disease (diphtheria, especially); in later years they may be associated with almost any disease, infectious or otherwise; they are occasional phenomena in a large proportion, if not the majority, of healthy adults. When numerous, their incidence is greatest in heart disease. Of the factors which appear to be predominantly associated with numerous extrasystoles, gross lesions of the heart (myocardial disease, coronary disease and mitral stenosis) unquestionably stand first. Excessive tobacco smoking may be responsible. Full doses of digitalis and its allies often induce them. There are clinical associations between premature contractions, raised arterial pressure, anemia of the heart and digestive disturbances (especially flatulence), but these are not fully understood at present. When the heart is predisposed, fatigue is a provocative cause; they are also especially frequent after exercise, when the heart rate slows; mental effort is also spoken of as an exciting cause. There is no special histological anatomy.

4. **Simple Paroxysmal Tachycardia.**—This is a condition in which from time to time the normal mechanism is abruptly submerged in rapid contractions of the heart chambers, responding to a regular series of new impulses. The normal pace-maker of the heart initiates its impulses at a rate of 72 per minute. If a new centre of impulse formation develops in some extraneous or ectopic focus in the musculature, and the impulses are formed serially and at a faster rate, then the new centre becomes the pace-maker, and dominates the movements of the whole heart. Such is the condition in simple paroxysmal tachycardia; the paroxysms consist of *sudden* accelerations of heart rate, and the contractions composing the paroxysm come from a series of new and rhythmic impulses, started in a fresh cardiac centre (auricular or ventricular). The change in the heart rate, both at the onset and offset of the paroxysm (Plate III, Fig. 3), is absolutely abrupt. The paroxysms vary in rate between 110 and 200 per minute; they may have a duration of a few seconds or may last a few hours, a few days, or a week or more.

Paroxysms of this kind have been induced experimentally by ligaturing branches of the coronary arteries and by the injection of those drugs which are known to give extrasystoles; the paroxysms are in fact probably composed of extrasystoles, arranged in a regular series.

In the human subject they may be definitely related to posture, occurring only while the patient stands, disappearing when he lies or when on standing the abdomen is compressed; a relation which suggests that they may be provoked by cardiac anemia. In quite half the cases no history of infectious disease is discovered, and in a large proportion of the patients, the heart seems otherwise almost normal. Of past infections rheumatic fever is alone common; occasionally malaria, scarlet fever and measles have been associated with the condition. Paroxysms are fairly common in patients who suffer from heart disease, especially those who show symptoms or signs of myocardial inadequacy and in those who present mitral stenosis. Where there is the predisposition, attacks are induced by exercise and emotion. Flatulent dyspepsia is a frequent association. A special histological anatomy is unknown.

5. **Auricular Flutter.**—Auricular flutter is a similar condition, and one which has been arbitrarily separated from the last, chiefly for clinical reasons. It is a condition in which the auricular rate is raised to between 200 and 340 per minute, and in which the ventricle beats at a slower rate (usually at one-half) (Plate IV, Fig. 1), though, as a rule, in response to the auricle. Acceleration and heart-block are combined therefore. Flutter, which is only known to arise in the auricle, may occur in short paroxysms; but more often it is a persistent condition, lasting for months or years when untreated. It is closely related to a condition presently to be described, namely, fibrillation of the auricles, and often passes over to it.

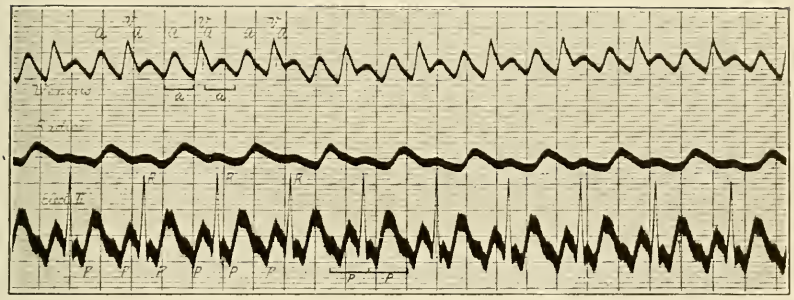
Of the pathology of the condition we know little, it may be produced by weak faradization of the auricle, and I have seen it after the injection of glyoxylic acid. Clinically it may be associated with rheumatic heart disease, but usually the heart shows no sign of disease beyond slight enlargement. A recent history of "influenza" has been spoken of in several cases; infections of the urinary tract may be present; it occurs for the most part in elderly subjects.

6. **Auricular Fibrillation.**—This is a condition in which the normal and coördinate systole of the auricle is lost and in which the musculature of this chamber contracts in a fibrillar fashion. The wall stands in a position of diastole and fine or coarse tremulous movements are seen over the whole of its surface. When the auricles are in this state, they send rapid and extremely irregular impulses to the ventricle. The movements of the ventricle are therefore grossly arhythmic, and the irregularity is so complete that the condition has been erroneously referred to as *delirium cordis*.

The auricles are readily fibrillated in experiment by faradization; they sometimes pass into fibrillation at stimulation of one or other vagus; the condition also occurs spontaneously in the heart under experimental conditions. With the exception of the faradic current, no certain means of producing it is known. We are in the dark as to the mechanism of its production in man.

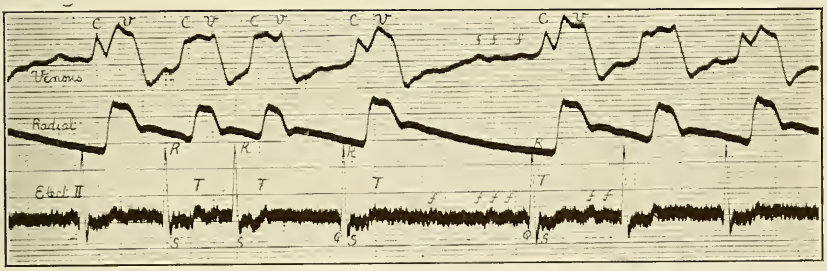
PLATE IV

FIG. 1



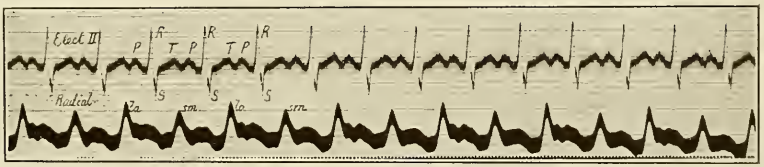
Venous, arterial, and electrocardiographic curves from a case of auricular flutter. × ⅔. The rate of the auricular contractions is 250; the rate of the ventricular contractions is 125 per minute. The ventricular contractions are easily distinguished by means of the summits *R* in the electrocardiogram, one of which occurs with each radial pulse beat. The auricular contractions are more difficult to distinguish; they are of very considerable amplitude, amounting to 6 millimeters, and are contiguous, giving to the electrocardiogram a very curious and characteristic appearance. The summits *R* arise from a base line which is constantly moving in a regular zigzag fashion. Each movement of this base line represents an abnormal contraction, but alternate movements are rather larger, because *T* falls with alternate *P* summits. The venous curve is also a complicated one; each cycle is accompanied by three chief waves, one of these is clearly an *a* wave, the two which occur together are a combination of *v* and a second *a* wave. A more detailed analysis is shown by the brackets underneath the curves.

FIG. 2



Simultaneous curves in auricular fibrillation. × ⅔. The radial curve is extremely irregular, the beats vary both in their incidence and their force. Each pulse beat has a corresponding elevation in the venous curve and this is of the plateau type. In the venous curve there is no *a* wave, whence it is called the "ventricular form of venous pulse," but in the long diastoles very fine oscillations appear; these are due to the fibrillating auricle. Similarly, in the electrocardiogram, the *P* summits are absent and are replaced by rapid oscillations, marked *ff*, due also to the fibrillating auricle.

FIG. 3



Simultaneous electrocardiographic and radial pulse curve, from a case of alternation of the heart. The alternation is clearly seen in the radial curve, a large (*la*) and a small (*sm*) beat succeeding each other alternately. It should be noted that the length of the large cycle is rather greater than the length of the small cycle. No alternation is visible in the electrocardiogram in this, as in most instances.

Fibrillation of the auricles (Plate IV, Fig. 2) is the commonest disturbance in the mechanism of the human heart; it also occurs as a rare event in the horse. In the human subject it is usually a sequel of rheumatic fever or chorea, or occurs in those who have mitral stenosis (50 per cent. of all cases of fibrillation). These cases form the largest or "rheumatic" group (70 per cent.), and the heaviest age incidence is between the twentieth and fortieth year. Fibrillation is also seen in senile affections of the heart, and especially between the ages of fifty and seventy years. It is not uncommon in heart disease in renal cases; it is less commonly associated with aortic disease. Fibrillation of the auricles is essentially chronic, once established it persists for the rest of life, but a small proportion of the patients exhibit it in a paroxysmal form, the attacks lasting a few hours or a few days. Fibrillation is occasionally encountered during the course of acute infectious diseases (rheumatic fever, diphtheria, and pus infections). The rate of the ventricle is extremely variable, according to the facility with which impulses pass to it from the auricle; usually between 110 and 150, the complete range of rate is 30 to 200.

The morbid anatomy is not distinctive; as a rule disseminated fibrosis and leukocytosis are found, the auricular tissues being the hardest hit and especially those regions which contain the highly differentiated tissues (the nodes and bundle); but hearts have been described in which these lesions were not found, and the same appearances have been seen where the mechanism was normal before death.

The Effect of Paroxysms of Fast Heart Action and Fibrillation upon the Circulation.—Simple paroxysms of tachycardia and paroxysms of fibrillation have similar effects upon the circulation. When the heart commences to beat more rapidly it decreases in size; the arterial and venous pressures move in reverse directions and the actual direction is governed by the arterial rate. Where the acceleration is great the arterial pressure falls considerably while the venous pressure rises; but with lesser degrees of acceleration the arterial pressures may remain steady or may actually rise a little. These are the immediate changes when the heart muscle is tolerably healthy. But in long-continued paroxysms, especially where the reserve power of the ventricular muscle is imperfect, the heart dilates, the fall of pressure is more profound and the blood stagnates in the heart and venous system. Fibrillation of the auricles, and simple paroxysms to a lesser extent, bring forth signs of cardiac failure, in the form of venous and liver engorgement and dropsy, when the heart is unable to accommodate itself to the increased burden which these disorders impose upon it. They do so, as I have said, chiefly by increasing ventricular rate; fibrillation affects the circulation in a minor degree by abolishing the mechanical function of the auricles; these chambers act as reservoirs, taking up the inflowing blood while the systole of the ventricles closes the circulation; in fibrillation the auricular contents are no longer emptied into the ventricles in diastole. This virtual paralysis of the auricles, with the accompanying stagnation of blood in them, predisposes to clotting in these chambers, especially in the appendices. Should they beat again coördinately the

clots may be detached and infarction follows. I have seen more than one case in which this order of events was distinctly suggested by the clinical symptoms.

7. **Alternation.**—Alternation of the heart is a condition in which, while the ventricles beat regularly, a large or small quantity of blood is thrown into the systemic circulation at alternate strokes of the pump; or in which the ventricles show alternate strong and weak beats (Plate IV, Fig. 3). It is manifested by hearts which are in a peculiarly weak condition, or, as it is termed, hypodynamic state, or by relatively healthy hearts which are heavily overtaxed.

Thus alternation is seen in experiment when the heart is severely poisoned with such drugs as aconitin, or by the products of asphyxia. Manifested by a ventricle which is not excessively burdened it is the sign of a dying muscle.

Alternation is met with clinically under a variety of circumstances. As a reaction to increased rate, it is seen in paroxysms of rapid tachycardia. When the heart rate is normal, it is often an accompaniment of advanced fibrosis of the ventricles or coronary disease. It is most frequent in the senile heart, in heart and renal disease combined, especially if arterial tension is raised or angina pectoris is prominent. When the heart is disposed to alternate, the occurrence of slight acceleration may disclose it; the occurrence of isolated extrasystoles has a similar effect.

Special Symptomatology.—Sinus arhythmias and the lesser grades of partial heart-block have no special symptomatology; these disturbances pass unnoticed by the patient. Similarly, in alternation of the heart, though symptoms are usually present, they are associations simply, and are not produced by the abnormal heart action.

Cardiac Syncope and Standstill of the Ventricle.—Cardiac syncope is a term which should, properly speaking, be confined to such attacks of loss of consciousness as come from deficiency in the action of the heart as a pump. It is probable that on the cardiovascular side, the most common cause of syncope is to be found in the bloodvessels; vasodilatation in the splanchnic area is the cause commonly assigned in accounting for fainting attacks in healthy people who manifest no signs of organic disease. A hutch rabbit faints when lifted by the ears; those people who have lax abdominal walls often experience giddiness upon suddenly assuming the erect posture. The faint is ascribed to cerebral anemia, following upon a temporary slack in the flow of venous blood to the heart. In aortic disease, in which attacks of giddiness or actual syncope are not uncommon, cerebral anemia is also regarded as the exciting cause, though the exact manner of its production is still unknown. All these subjects are particularly prone to the attacks while in the erect posture, and the assumption of the horizontal position brings relief; and it may be that in the aortic cases, as in those just cited, vascular disturbances are chiefly responsible. A compensatory spasm of the arteries of the lower limbs is believed by Leonard Hill to be a common phenomenon, whereby cerebral anemia in aortic disease is ordinarily held in abeyance. We require more extensive observations upon these forms of syncope.

On the other hand, there are certain forms of syncope in which the pathology is more fully understood. They are the most notable forms of what may be unhesitatingly termed *cardiac syncope*. They are eventually the direct result of cerebral anemia, and are all brought about by deficiencies in the action of the ventricles. If the arteries to the head are compressed (in man compression of the carotids suffices), the face blanches and in a few seconds the subject becomes giddy and a little later loses consciousness (Kussmaul and Tenner). More prolonged compression results in deep sighing respiration and convulsions. The same phenomena are seen in profuse hemorrhage.

If the ventricle ceases to throw blood into the arterial system, precisely the same symptoms follow; if the ventricle ceases to beat for from three to seven seconds, or if the rate falls to 8 to 20 beats per minute, unconsciousness results. After asystole of some fifteen or twenty seconds' duration, the veins become distended and cyanosis, stertorous respiration, and a twitching of the face and upper limbs are added to the symptoms. The heart fails to transfer the incoming blood from the venous to the arterial side (1) when the ventricles cease beating (true asystole), and (2) when the ventricles beat very rapidly.

1. *Ventricular asystole*, happens in one of three known ways:

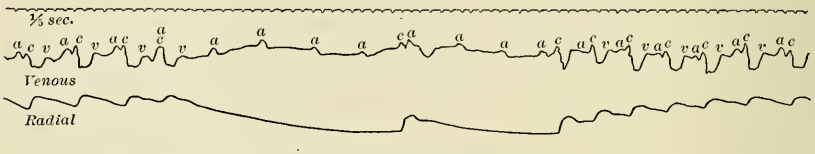
(*a*) In rare cases in which there is a disturbance of impulse production (see page 83). The whole heart beat is suspended in this condition, which is probably of vagal origin in most instances.

(*b*) In cases of heart-block. In those patients who suffer from high grades of partial heart-block or in those in whom complete dissociation is present, attacks of giddiness, of momentary loss of consciousness, of longer unconsciousness with cyanosis and epileptic manifestations are very common. In the fits the ventricular action is extremely slow or ceases for shorter or longer periods; the auricles continue to beat. The severity of the attack is conditioned by the degree of slowing or by the length of time over which the ventricular beats lapse. Death results when the ventricular asystole is of from one to two minutes' duration. In heart-block the attacks may be absent or infrequent, occurring at intervals of many months or years. In other patients they are more frequent, coming weekly or daily, or occurring successively over periods of several hours or several days and producing a picture of *status epilepticus*. As a rule the patient has no warning of an impending fit; though on occasion a perliminary pulse slowing or momentary periods of giddiness may serve as signs of the approaching danger; the sensations at the commencement of long seizures are similar to those accompanying a brief cessation of heart beat and do not properly constitute an aura. Incontinence of urine and tongue-biting are extremely rare, and a knowledge of this fact aids diagnosis; the petechial hemorrhages which occur in true epilepsy are not found. If the patient is seen in the attack its nature is recognized by the slow ventricular action and by the signs of the auricular contractions which are visible in the veins of the neck.

The fits of partial heart-block are the result of temporary increase in the degree of block. Repeated cardiac syncope is also seen as an infrequent manifestation in temporary and recurring attacks of heart-

block (Fig. 1). The period during which partial is developing into complete block is one of special danger to the patient. In some cases the increase of heart-block seems to have been of vagal origin and atropin has given relief. The cause of the convulsions in most cases of complete heart-block is unknown; it is of interest to note that exactly comparable attacks were witnessed by Erlanger in his experiments upon dogs.

FIG. 1



Venous and radial curves from a patient who suffered from numerous and short attacks of cardiac syncope. × ½. The curves show the nature of the attacks. The ventricular contraction ceases first for five seconds, then for three seconds; the whole period of disturbance being associated with a loss of consciousness. The normal heart action is then resumed. During the period of ventricular slowing, the auricle continues to beat at its former rate. The syncopal attacks were due to the sudden onset of temporary heart-block.

(*c*) Asystole may be the result of *fibrillation of the ventricle.* A possible instance of a temporary disturbance of this kind, resulting in cessation of the arterial stream, has been recorded by Hoffman. As a cause of convulsions in the human subject it must be extremely rare; as a cause of sudden death it is probably common, and from this standpoint it will be described and will receive further consideration at a later stage (see page 106).

2. *Rapid Action of the Ventricles.*—Several instances of loss of consciousness produced by extremely rapid action of the ventricles are upon record (Wenckebach, Gossage). With great acceleration of the ventricle, or with lesser acceleration when the circulation is failing, little or no blood is forced into the arteries; the blood pressure falls toward zero and consciousness is lost. The attacks to which the subjects of auricular flutter are prone are ascribed to this cause. As a rule the ventricular action is much slower than the auricular in this condition, but occasionally the ventricle beats at the same rate as the auricle, and the acceleration may be as much as 290 or 300 per minute; in these circumstances consciousness may be lost.

Adams-Stokes syndrome is a term which has been applied to attacks of syncope or epilepsy associated with habitually slow pulse action. As a rule the association is due to the presence of heart-block; but slow action of the ventricle may result from slow action of the whole heart, and this may be combined with similar attacks or with momentary seizures of extracardiac origin. Several cases are on record also in which in true epileptics the *pulse* was slow for long periods, because extrasystoles were present (see page 85). These variations in the clinical picture and the diverse causes of syncope generally, emphasize the need of exhaustive study wherever the nature of convulsions is not abundantly clear.

The Symptoms of Premature Beats.—In a large number of affected patients the abnormal beats pass unperceived. On the other hand these premature beats constitute one cause of what patients term "*palpitation.*" The symptom is more prominent in the young and especially in those of female sex and in those of nervous temperament. The intermittence awakens a feeling of uneasiness or oppression in the chest, or a feeling of void, while the succeeding contraction is accompanied by consciousness of shock to the chest wall and often by a feeling of gripping in the throat. By calling attention to the heart they induce anxiety. The sensations are exaggerated by general depression of the health, by fatigue and by emotion. They are often more noticeable at night, after excessive smoking, after a heavy meal, or after exertion. When numerous they may occasion actual distress, especially if they are grouped together; anxiety may be profound under these circumstances and faintness, coldness of the extremities and sweating may result.

The Symptoms of Paroxysmal Tachycardia.—The symptoms in simple paroxysmal tachycardia, in paroxysms of flutter and in paroxysms of fibrillation are alike. In a given patient the length of the paroxysms is fairly constant; in some they are infrequent and of long duration; in others they are frequent and of short duration. The symptoms are controlled by the length of the paroxysm, by the rate of the heart beat during them, by the state of the heart muscle, and by the tone of the nervous system; they are consequently very variable. In short and relatively slow paroxysms there may be no symptoms and in longer and more rapid attacks they may be severe.

The immediate onset is signalled by discomfort in the region of the heart, which may amount to slight or violent palpitation. A sense of tremor or fluttering in the chest, a beating in the neck, is common. Lassitude, exhaustion, coldness and sweating are early symptoms. Later, flatulence, nausea and vomiting may be prominent. The alimentary symptoms, once established, persist till the attack is over; they hasten the exhaustion which is conspicuous in attacks of long duration. In many patients anginal symptoms are added, varying in intensity from soreness of the chest and a sense of compression, to violent and radiating pains. Symptoms and signs of cardiac embarrassment are often seen and increase as the attack proceeds. The limits of dulness and the orthodiagraphic outline, at first diminished, increase progressively during the course of the attack. To pallor, which is often conspicuous at an early stage, cyanosis is added, the eyes seem sunken and dark areas appear around them. The veins and liver swell gradually, and tenderness and pulsation are found over the last-named organ. Aching pain develops in the epigastrium and hypochondrium. A cough, accompanied by frothy and at last blood-stained expectoration, develops with signs of bronchitis or congestion and œdema at the bases of the lungs. Collapse is prominent in the later stages; the attack may terminate in progressive failure, delirium, ascites, general anasarca and death. Unexpected death terminates the paroxysm on occasion, but in most instances there is an abrupt recovery and this may come at any moment. The cessation is marked by symptoms of its own, a sharp, stabbing pain,

one or more forcible shocks of the heart. Usually the patient speaks only of relief. The rapidity with which the symptoms and signs vanish is remarkable. The dilated veins and heart contract in size, the liver recedes less rapidly below the ribs. Quantities of flatus are expelled and limpid urine is often voided after an attack. For several days there may be exhaustion and soreness of the chest.

Stasis in the lungs during paroxysms, with dulness and crepitations at the bases, has been mistaken for pneumonia. Severe abdominal pain, anginal or hepatic, with conspicuous collapse and running pulse have been mistaken for perforated gastric ulcer. A large number of the cases have been carelessly grouped as instances of "acute dilatation" or "heart strain," especially when paroxysms have succeeded unwonted efforts (see remarks on Dilatation and Tachycardia, page 82). Forcible beating in the veins of the neck, with a distension of the jugular bulb on the right side may closely simulate innominate aneurism.

Symptoms in Continued Flutter and Fibrillation of the Auricle.—In patients in whom auricular flutter or fibrillation is continuous, the symptoms vary, as in paroxysmal tachycardia, according to the rate of the ventricular action, the state of the heart muscle and nervous system. In many patients they create little disturbance, in these the ventricular action is slow and the muscle relatively strong. In others dilatation of the heart, engorgement of the veins, cyanosis, enlargement of the liver and dropsy appear and persist. These are cases in which the rate is rapid and the muscle fails to meet the added burden.

Thus the symptoms are largely those of a degenerate and failing heart muscle, symptoms which may come in the absence of flutter and in the absence of fibrillation. They are promoted by rises of ventricular rate when the muscle is already fully taxed; and therefore, frequently appear when flutter or fibrillation appears, persisting so long as the increased rate is maintained. If the muscle is less degenerate, or, what amounts to the same thing, if it is less heavily burdened beforehand, the appearance of these disorders may give rise to no serious circulatory embarrassment. The importance of flutter and fibrillation from the clinical standpoint lies in the rate which they engender in the ventricle. A degenerate muscle is unable to tolerate the strain of greatly enhanced rate.

Clinical Types: Clinical Distinction of Pathological Types.—Preliminary Evidences.—*Incidence.*—In hospital practice auricular fibrillation is responsible for the largest number of irregular hearts; premature contractions are almost as frequent; the remaining disorders are much less frequent.

Age and Frequency.—Irregularity in young children is almost always of sinus origin; premature beats and heart-block have been described but are rare in early years; fibrillation of the auricles is almost unknown before the age of thirteen, and is extremely rare before the seventeenth year.

Heart Rate.—When the ventricle is regular in its action and its rate is below 35 per minute, complete heart-block is usually present (Plate II, Fig. 2); a rate of 40 to 50 suggests partial heart-block. A persistent heart

rate of 130 and over should always bring a long-continued paroxysm of tachycardia to mind. *If the ventricle beats irregularly* and the rate surpasses 120, fibrillation is generally present; and as the rate is faster so the diagnosis becomes more certain. Premature contractions are rarely seen at heart rates of 120 and over; sinus arhythmias are almost confined to rates below 100.

Persistence of Irregularity.—Auricular fibrillation is the only disorder in which the action of the ventricle is permanently irregular. All other irregularities are transient, or broken into from time to time by periods of regular action.

Common Clinical Types and their Meaning.—*Intermittence of the Pulse.*—An occasional long pause in an otherwise regular pulse is due to one of two causes; namely, a premature contraction which fails to affect the arteries, or a failure of the ventricle to respond to an auricular contraction (heart-block).

Coupled Beating and Triple Beating (Bigeminy and Trigeminy).—These phenomena are due similarly to premature beats (Plate III, Fig. 1) occurring at regular and frequent intervals or to heart-block (Plate II, Fig. 1), frequent ventricular responses being missed at regular intervals. *Halved pulse rate* may be due to halved ventricular rate or to premature beats replacing each second normal beat and themselves failing to reach the pulse.

Halved Ventricular Rate.—A sudden and exact halving of ventricular rate is always due to heart-block.

Regular tachycardia may result from simple acceleration, simple paroxysms of tachycardia or auricular flutter.

Irregular tachycardia and gross irregularity of the ventricle, both in the rhythm and force of its contractions, are almost always the result of auricular fibrillation; exceptionally they may be due to frequent premature contractions or to heart-block, especially when the latter is associated with flutter.

While different forms of disordered action may often be recognized by simple bedside tests, the exact diagnosis of a particular disorder ultimately depends upon the employment of graphic records. By polygraphic or electrocardiographic means, the relative positions of the contractions in auricles and ventricles may be identified and compared. Those who desire full information and descriptions of these methods should refer to special treatises dealing with them. The signs by which the chief forms of altered heart action may be identified are set forth in the following paragraphs:

Clinical Distinction of Pathological Types.—*Simple Tachycardia.*—When the ventricular rate is raised and the enhanced action is a simple acceleration of the whole heart:

(*a*) The rate is greater after exercise, with emotional disturbances, in the erect posture, and after the administration of such drugs as atropin.

(*b*) It falls considerably during the first few hours or days after the patient takes to bed; it falls by 10, 20, or 30 beats per minute when the erect posture gives place to a horizontal one.

(*c*) The rate is rarely over 140 while the patient rests in bed.

(*d*) The rise of rate is gradual, its fall is equally gradual, the rate varies considerably from time to time.

(*e*) There is as a rule no reaction to digitalis.

(*f*) Electrocardiograms are of normal outline (see Plate I, Fig. 1).

Simple Paroxysmal Tachycardia.—This form of acceleration is recognized in the following manner.

(*a*) The rate is almost constant with exercise and under emotional changes.

(*b*) It varies little, if at all, with posture.

(*c*) The ventricular rate often exceeds 140, and may remain at 200 per minute even after the patient has reclined for hours or days.

(*d*) The onset of the tachycardia is abrupt; its offset is equally abrupt.

(*e*) It rarely lasts more than ten days; it may last but a few seconds.

(*f*) Digitalis produces no slowing and no irregularity.

(*g*) The electrocardiograms show an equal rate of auricle and ventricle, and an abnormality in the seat of production of the beats. These may arise in the ventricle or in an ectopic auricular focus (Plate III, Fig. 3).

Auricular flutter usually occurs in elderly subjects. When the ratio of contraction of auricles and ventricles is as two to one:

(*a*) The ventricle beats regularly at rates varying between 100 and 165.

(*b*) In a given case the ventricular rate is constant under a variety of circumstances, as in simple paroxysms.

(*c*) The onset and offset are not witnessed, but are spoken of as abrupt. The duration is usually several months or years.

(*d*) Digitalis always produces slowing and irregularity.

(*e*) Pressure upon the carotid sheath and vagus has similar results.

(*f*) In the veins of the neck, extremely rapid undulatory movements are often to be seen and may be recorded (Plate IV, Fig. 1).

(*g*) Electrocardiography shows two auricular contractions to one ventricular and an auricular rate of from 200 to 340 per minute (Plate IV, Fig. 1).

When the ratio between auricular and ventricular contractions is greater, the diagnosis is more difficult, but:

(*a*) The rapid undulations in the jugular vein are often conspicuous.

(*b*) Occasionally the rapid auricular contractions can be heard with the stethoscope.

(*c*) If the pulse is regular at 70 or 80 per minute, it will rise abruptly to exactly double this rate with exercise.

(*d*) If the pulse is irregular, the beats are curiously grouped and the same phase of irregularity is frequently repeated. It becomes regular with exertion or atropin.

(*e*) Electrocardiograms will always identify the rapid auricular movements.

Sinus irregularity is easily recognized:

(*a*) It is specially prominent in children.

(*b*) The rise and fall of pulse rate is periodic and accompanies the natural or deepened acts of breathing.

(*c*) A rise of heart rate, from whatever cause, gradually abolishes the irregularity, which is very unstable.

(*d*) Polygraphic and electrocardiographic curves show the auricle and ventricle to participate equally in the irregularity. The electrocardiograph demonstrates that each heart beat arises normally (Plate I, Fig. 2).

Simple Bradycardia.—In simple bradycardia:

(*a*) The ventricular rate is rarely less than 50 per minute.

(*b*) Pulse and ventricle beat at the same rate; the rate rises with exercise and falls again subsequently.

(*c*) The movements of the veins are synchronous with the several heart beats. Polygraphic curves show auricular and ventricular waves in their normal sequence.

(*d*) The electrocardiograms are normal except that the groups of deflections are widely separated.

Partial Heart-block.—In this condition:

(*a*) The heart's action is intermittent or grouped.

(*b*) The rate of ventricle and pulse is the same and the irregularity is parallel in both.

(*c*) The ventricular rate often lies between 40 and 50 per minute.

(*d*) All irregularity is abolished by exercise and usually by atropin.

(*e*) Abrupt changes of ventricular rate to a half or double the former rate are apt to occur.

(*f*) In polygraphic and electrocardiographic curves the auricular contractions are more numerous than the ventricular ones (Plate II, Fig. 1).

Complete Heart-block.—Where dissociation exists:

(*a*) The ventricular rate has usually fallen to 30 per minute or thereabout. The ventricle beats regularly and its rate is uninfluenced by exercise or atropin.

(*b*) Attacks of giddiness or loss of consciousness are usually to be found in the past history.

(*c*) Auricular waves may be seen in the veins of the neck, occurring during the long diastoles. The venous pulsation often waxes and wanes independently of respiration. The auricles may be seen to beat more rapidly than the ventricles on the fluorescent screen.

(*d*) The heart sounds are peculiar; a first and second sound is heard with each ventricular systole, but these sounds vary in intensity in an extraordinary manner or show varying reduplications from cycle to cycle. The auricular sound, very distant and muffled, may often be heard over the auricles or at the apex beat or epigastrium.

(*e*) In polygraphic and electrocardiographic curves, the auricular and ventricular movements are regular but at distinct rates, the auricular rates are those of the normal heart beat or somewhat in excess of it. Auricular and ventricular contractions frequently coincide (Plate II, Fig. 2).

(*f*) Very frequently minute waves may be seen upon arterial curves (Plate II, Fig. 4).

Premature contractions are easily recognized because:

(*a*) They are responsible for intermittence of the pulse and for most instances of grouped action of ventricle and pulse.

(*b*) The rate of ventricle and pulse is usually different. Many of the premature beats fail to affect the pulse. When the pulse is intermittent, single premature beats are palpable or audible at the apex beat. The ventricular rate may be double the pulse rate. If the pulse beats in paired fashion, the ventricle often beats in groups of threes.

(*c*) The heart sounds are often peculiar. Those premature beats which fail to reach the wrist are accompanied by first sounds only and these are premature sounds. The heart sounds (first and second) are heard in groups of three or four sounds when the pulse beats are coupled.

(*d*) Premature beats are abolished by rises of heart rate.

(*e*) They are readily identified in polygraphic curves, and are seen to come, some from the auricle, some from the ventricle (Plate III, Figs. 1 and 2).

(*f*) In electrocardiograms the pictures are even more characteristic. These beats arise in abnormal foci; the contractions run along abnormal paths in one or other heart chamber and often give rise to highly abnormal pictures (Plate III, Figs. 1 and 2).

Auricular fibrillation is distinguished because:

(*a*) It is usually associated with signs of serious heart failure, and occurs in young adults and elderly people.

(*b*) The pulse and ventricular action are grossly irregular (Plate IV, Fig. 2), and the rate is generally increased (110 to 150).

(*c*) The irregularity is persistent and is uninfluenced by those events which raise the heart rate under normal circumstances.

(*d*) The ventricular rate is usually conspicuously affected by digitalis.

(*e*) In cases of mitral stenosis, with which it is commonly associated, an isolated presystolic murmur is not heard; and if the ventricular rate is slow this murmur is replaced by an early diastolic murmur.

(*f*) In polygraphic curves the "ventricular form of venous pulse" is found, that is to say, there is no sign of a presystolic wave resulting from auricular contraction. The fibrillating auricle may give rise to fine oscillations on the curve in long diastoles (Plate IV, Fig. 2).

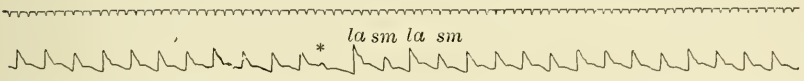
(*g*) The electrocardiograms show no sign of coördinate auricular contractions. The normal auricular summits are replaced by characteristic oscillations which run throughout the whole curve and are especially prominent in diastole (Plate IV, Fig. 2).

Alternation of the Heart.—This condition is occasionally recognized in estimating systolic blood pressure; alternate beats force their way through the armlet at higher pressures. Usually it is found only when deliberately sought in arterial curves (Plate IV, Fig. 3). It is wise to examine with the sphygmograph cases of angina pectoris, all cases of high blood pressure and all elderly subjects in whom affections of the heart are suspected, or in whom renal disease is known to exist, with the specific object of determining the presence or absence of alternation of the pulse. It should be sought also after premature beats (Fig. 2) in all elderly subjects and in all cases of heart disease.

Prognosis.—In dealing with cardiac patients, prognosis occupies a prominent place. We are asked to foresee the probable duration of life under given circumstances; we are expected to foretell the measure in

which our patients will suffer from subjective disturbances and if and when these will subside. Lastly, we have to determine the possibility or probability of sudden and unexpected death. We are asked much; with careful study and deliberation we can prophesy a little.

FIG. 2



An arterial curve showing the appearance of alternation of the pulse for two short periods after the occurrence of a single extrasystole. × ¾. The extrasystole is marked with an asterisk.

The forecast in patients who complain of cardiac symptoms is based upon a number of considerations.

1. Our first duty is to ascertain, where this is possible, if disease of the heart is the primary fault and carefully to exclude such disturbances of the circulation as are the result of organic or functional defects in outside organs.

2. If it is in the heart itself that the primary weakness is discovered, or if the heart has been seriously and permanently damaged by coexisting disease in other organs, we must first attempt an estimate of the strain which the organ has to bear. It may be that the heart works at a disadvantage, that it has to force the blood through a constricted orifice, or that it is unable to choose its own and suitable rate of beating. The burden may be smaller than, equal to, or greater than, normal.

3. We should endeavor to arrive at an idea of the functional efficiency of the muscle, and especially that of the ventricle, considering particularly the degree of reserve, its plenitude or its limitation. And we should consider the efficiency from the standpoint of the work to be accomplished and the circumstances under which this work is undertaken.

4. We must ascertain, where we can, the probability of change in the relations between work and efficiency for work in the near future. Is the disease stationary or progressive? Will the efficiency increase with appropriate treatment? In respect to the latter, it may be wise to delay a full statement until the effects of such treatment are seen or the course of the malady under treatment begins to be evident.

5. Lastly, we must be fully acquainted with the progress of symptoms in the several disorders and have particular knowledge of those in which sudden catastrophies occur at all commonly.

Prognosis in any given case takes us therefore over a wide field. Our present purpose is to inquire whether we are aided by recent observations upon disorder of the heart's action; and if so, in what direction and to what extent? We shall find they aid us very materially and in many directions.

It is essential to recognize that prognosis in heart affections cannot be based upon what we regard as the probable macroscopic and microscopic lesions. Prognosis upon a purely anatomical basis is insufficient; speaking generally, at the present time the reason of death is not revealed by the dead organ. While anatomical and mechanical reasoning has occupied

the foreground of the argument, this argument has been incomplete. Observation of the heart as a living and moving organ; study of its movements, be they normal or perverted, by exact methods; observation of the reaction of the heart to altered conditions, form the readiest paths to the desired information.

Tachycardia.—To discriminate between the varieties of tachycardia is the first essential. The heart rate may be raised, its action may be regular or irregular. At present we may consider the former. As we have seen, regular tachycardia is of three varieties; they have been termed simple tachycardia, simple paroxysmal tachycardia, and auricular flutter. The prognosis, like the treatment, is different in the three states.

Simple Tachycardia.—Having determined the presence of a simple tachycardia, attention should no longer centre upon the heart. The rapidly beating organ is but an indicator, telling of a disturbance of innervation or of an altered physical or chemical environment. The discovery of an enlarged thyroid, signs of intoxication, a focus of infection or instability of the nervous system, reveals the cause of the acceleration and guides prognosis. It should not be forgotten that simple acceleration may accompany disease of the heart itself, and this has to be taken into account in the prognosis of mitral stenosis and of aortic disease.

Simple paroxysmal tachycardia should for the present be regarded as primarily a cardiac condition. The prognosis of the individual attacks contains an element of uncertainty. Death during paroxysms is not very infrequent in the affected, but considering the attacks themselves, this termination is rare. The severity of the symptoms is influenced largely by the reaction of the nervous system; neurotic people awaken undue anxiety. The duration of the observed paroxysm and the length of previous paroxysms have to be considered; the duration is fairly constant in a given case; the paroxysms generally terminate before a week or ten days have passed, usually they last a few hours. They are but rarely terminated by treatment. The outlook is more ominous when, after several days, the heart still shows signs of progressive failure and when œdema of the lungs, delirium and dropsy appear. Nevertheless it often happens that at the height of the embarrassment the paroxysm ends and relief is immediately obtained.

The prognosis of the malady as a whole is based upon an estimate of the endurance of the cardiac muscle between the attacks and upon the severity of the attacks. The first prognostic evidences are the same as in a similar case where there are no attacks, with the following reservations. The attacks are themselves indications of muscle damage and they may jeopardize the life of the patient. The reaction of the heart to the attack is important. A healthy heart reacts to increase of rate by decreasing in size, and if the acceleration is not extreme, the circulation may be maintained for long periods. A diseased ventricle reacts after a short while by dilating. The degree of dilatation, the rapidity of its onset and progress suggest the degree of muscular involvement. Secondly, the severity of the attacks in respect of duration, frequency, and rate of the heart's action is summed up; but as the attacks may cease at any time, never to return; and as we do not know to what extent

paroxysms damage the heart, if they damage it at all,[1] the value of these considerations in completing the prognosis is limited. The possibility of unforeseen death in a paroxysm necessitates caution in prognosis.

Patients inquire as to the prospect of the attacks ceasing; in young subjects, if the heart is sound while it beats normally, they may be told that, while freedom cannot be promised, the prospect of it is fair.

Auricular Flutter.—When flutter develops, it throws an increased strain on the heart, proportioned to the increase of ventricular rate. Untreated it is usually a persistent condition. If the muscle is degenerate and the rate rapid, signs of failure supervene and if unrelieved the patient's condition is precarious. On the other hand, when it occurs in a tolerably healthy heart, much circulatory embarrassment may not be manifest. The influence upon the life history under these circumstances is not fully known; though its persistence for three years has been recorded, the ventricle beating continuously at 150 per minute, or more. It is a condition which often reacts in splendid fashion to treatment; the forecast is more readily accomplished after this has been undertaken. If it is abolished by treatment, it may or may not return, but in the last event further treatment is successful.

Auricular Fibrillation.—As in other kinds of arhythmias, the prognosis is governed largely by the remaining signs, and especially by an estimate of the strength and reserve of the muscle. But fibrillation is itself a sign of muscle involvement; occurring in acute illnesses it indicates invasion of the myocardium; as a chronic condition it is generally associated with disseminate and chronic inflammatory lesions, leading up to diffuse fibrosis. Fibrillation of the auricles loads an already defective muscle with an extra burden, the burden of increased ventricular rate and shortened diastole. It heralds cardiac failure, temporary or permanent; very few patients survive its onset for more than ten years; as a rule the end comes more speedily. The grade of acceleration which it imposes upon the ventricle, the reaction of the ventricle to this acceleration, and the degree in which the acceleration may be controlled by appropriate remedies, form the chief prognostic considerations. A high rate of ventricular contraction, much dilatation of the ventricle, the absence of conspicuous response to digitalis, combine to form a grave picture, and indicate an early dissolution. A lower rate, or the ready control of rate by digitalis, is more favorable, especially the former. The retention of the normal limits of heart dulness, or the presence of but slightly increased limits, when the rate is fast, points clearly to considerable reserve in the ventricles. The prognosis in paroxysmal fibrillation is similar to that in simple paroxysmal tachycardia, with the reservation that such patient more frequently develop permanent fibrillation than do the subjects of the simple attacks.

Slow Action of the Ventricle and Heart-block.—*Simple Bradycardia.*—As in the case of simple tachycardia, the prognostic significance of slow action depends upon the cause, and this is usually extracardiac when

[1] The question of strain and its effect upon the heart has long been the subject of controversy; of all the strains to which the heart is submitted none are so severe or of such long duration as some of these paroxysms, yet they seem to leave no aftermath.

the rate lies between 50 and 70. It is probable that where the pulse rate lies between 30 and 45, the cause is as a rule intracardiac; yet such patients progress favorably, providing that signs of muscle efficiency are present. Of the relation of *vagal standstill* to the life history we have incomplete knowledge. The patients may show complete recovery. Death as a result of vagal inhibition of the heart's action has not been proved, neither has its existence been shown to be probable; where the muscle seems healthy, and no gross disease affecting the vagi can be identified, the patient should be reassured.

Heart-block.—Those who die exhibiting heart-block usually die with signs of general heart failure. It will be understood that heart-block and the Adams-Stokes syndrome are by no means synonymous terms and that most subjects of heart-block never have convulsions; the lesser grades of heart-block are by far the commonest and are frequently associated with rheumatic heart disease. Where partial heart-block is persistent there are usually other signs of cardiac involvement; the presence of heart-block gives an added significance to the case. It is an evidence of myocardial damage, not necessarily limited to the conducting tract, but usually disseminated throughout the more silent areas of the muscle.

Partial block which is temporary is often associated with acute infectious disease, as in rheumatic fever and pneumonia. Occurring in these conditions it is a sign of the gravity of the infection; it may be the sole indication that the myocardium has been damaged. Occurring in patients who suffer from rheumatic heart disease, it is to be regarded as an outward sign of an isolated injury which, if repeated, eventually so weakens the muscle that life is no longer supported.

In the higher grades of block, in addition to the general evidence of integrity of the muscle or the reverse, the convulsions have to be taken into account. Some patients are free from them, in others they are frequent and severe. Those patients especially in whom the lesions are progressive and in whom partial is passing to complete block, must pass through a time of particular danger, for then convulsions are often frequent. Regarded in its entirety, persistent heart-block of high grade is a grave condition. The bundle defect is usually complicated by other muscle lesions and the mortality is very heavy. The ease with which autopsies have been obtained in these patients speaks for the seriousness of the malady. Nevertheless, some patients survive in comparative or absolute comfort for many years. They are for the most part young subjects, and those in whom the remainder of the heart muscle is comparatively healthy.

Sinus Arhythmia and Premature Beats.—*Sinus Arhythmias,* with the exception of standstill of the heart, have little or no prognostic significance. In young subjects these irregularities are to be regarded as normal phenomena; if they are recognized they are not confused with more serious disturbances. Irregularity of the heart has long been regarded as ominous; today we know that certain irregularities are of no consequence in prognosis.

Though *premature beats* are decided evidences of pathological defects

in the heart; yet while they are so common in apparently healthy subjects, and while they may persist from early to advanced years, they cannot be said seriously to affect prognosis. The heart is quite healthy in but a few adult subjects living under modern conditions; the significance of slight changes in the muscle must be regarded from the comparative standpoint. The sole reservation in regard to premature contractions applies to their occasional presence as precursors of paroxysms of tachycardia or of permanent auricular fibrillation. In the great majority of those patients in whom they are seen, the more serious disorders will not develop.

Alternation of the Heart.—The gravity of the malady in a patient who exhibits this sign is often borne witness to by the association of angina, nocturnal dyspnœa, Cheyne-Stokes breathing or high blood pressure. But its special value lies in the fact that while each and all of these symptoms may be absent, alternation may be present and foretell the future. Accompanying a normal or slightly enhanced heart rate it speaks clearly of muscle exhaustion. If continuously present, a favorable prognosis is always forbidden and such a forecast is rarely justified when it appears even temporarily in the pulse. The only propitious circumstances, when it is seen, are a history of exceptional and prolonged strain, which may be immediately avoided for the future, and evidences of acute intoxication which are disappearing.

Treatment.—Treatment, dictated by the rate and mechanism of the heart's action, is directed by a few clear principles.

1. The nature of the disturbance being recognized, we are often able to decide whether it is the heart which is primarily at fault, or whether a healthy musculature is merely responding to abnormal influences, be they nervous, chemical or physical.[1] Our first endeavor is to locate the mischief, either in the heart or outside it, and to treat our patient accordingly. If the musculature can be declared healthy, the heart is no longer our chief concern. If the heart is itself involved, then:

2. We search for etiological factors, and especially for the source or channel of an infection; we remove the former or seal the latter, and in this fashion we may be successful either in cutting short the whole disturbance or in preventing or retarding its progress. In rare instances we may treat an infection by specific measures.

3. In the cases of periodic disturbances, we guard against the provocative causes of such crises.

4. When the disturbance is an established one, we may at times employ such remedies as abort it; more frequently treatment will resolve itself into:

[1] Our knowledge of the pathology where there are disorders of sequence is still incomplete; in dealing with simple tachycardia we may assume an extracardiac origin of the disorder in almost all instances; it is not so clear that simple paroxysms of tachycardia or fibrillation or profound slowing may not be of purely nervous origin. Still we require a definite basis for therapeutic measures and today it seems improbable that the named disturbances arise when abnormal nervous impulses play upon the healthy organ; it is more probable that they appear when the heart responds in an abnormal fashion to such impulses. There is an evident overlapping on the chemical side; abnormal nutrition or poisoning may certainly be responsible for both simple sinus disturbances or actual disorders of sequence.

5. Adjusting a proper relation between the work which the heart has to do, and its capacity for such work; and thereby prolonging the life of the subject. There remain:

6. Remedies employed for the relief of symptoms.

7. Precautionary measures for the avoidance of sudden catastrophes.

Simple Tachycardia.—The treatment of simple tachycardia requires little discussion. It is controlled by knowledge of its cause, and the remarks which have been made under diagnosis and prognosis are sufficient guides to treatment which is considered in detail in other chapters of this system.

Simple Paroxysmal Tachycardia.—The treatment resolves itself into that applied during the crisis and the care of the patient during the general course of the malady.

We are aware of no unfailing remedy which will abort the attacks. Some few patients are able to terminate the seizures by assuming a peculiar posture, by taking deep breaths or by inducing vomiting. Deep pressure applied successively on the right and left carotid sheath should be tried; in a number of recorded instances the paroxysms have terminated as a result and the procedure is without danger. The application of an ice-bag to the precordium, a remedy which always affords relief, may speedily bring the desired ending. I have seen attacks terminate after single injections of digitalis or strophanthin, but regard these as uncertain remedies. The application and retention of a tight abdominal binder sometimes serves in abolishing numerous attacks each of a few seconds' duration. Usually, radical treatment is of no avail, and the remedies relied upon are palliative. Rest is enjoined, though the wishes of the patient in respect of posture are considered. In severe attacks sudden movement of any kind is forbidden and it is advisable that the patient should be fed by hand and that the bowels should be cleared by simple enemata in paroxysms of long duration. The dietary should be fluid, bland and as restricted as possible. Iced water or milk, albumin-water or beef-tea are suitable. Local applications, the ice-bag, mustard plaster, leeches or cupping, applied over heart or liver, according to the seat of pain, often bring relief. Severe pain may be treated with chloral or morphine; and these remedies may also be used to induce sleep which is often deficient; the encouragement of sleep is always clearly called for. Great engorgement of the heart, or the appearance of engorgement of the lungs or dropsy, suggests venesection. The letting of eight to sixteen ounces of blood will be followed by improvement; but the occasion for it does not often arise. Simple expectorants may be used for the cough. Pure oxygen is administered when there is deep cyanosis.

In treating the malady as a whole, a searching inquiry may reveal exciting causes of the paroxysms, which may be removed; sudden emotion or exertion may be the chief provocative factor, and it may become necessary to interdict active employment. The relief of oral and pharyngeal sepsis, the remedying of dyspeptic troubles, and detailed attention to the general habits of the patient, the moderation or banning of tobacco, alcohol and sexual excitement, are important considerations. Eventu-

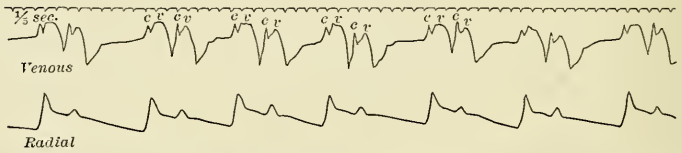
ally and in long-continued paroxysms, a full course of digitalis may be advisable.

Auricular Flutter.—When of temporary duration the treatment of this condition is similar to that of simple paroxysmal tachycardia. Persistent flutter is treated with drugs of the digitalis group. If the course of the drug administration is carefully supervised by graphic methods, notable successes are often achieved. Digitalis in the form of the tincture or infusion is given in stiff doses: ♏x to xv (0.6 to 1 cc.) of the tincture; ℥j to ij (4 to 8 cc.) of the infusion, until, as always happens, when the ventricular rate is originally rapid, ventricular slowing is obtained. According to the needs of the patient the drug is pushed further until the ventricular rate falls to 70, 60 or 50; the dosage may then be reduced and regulated so that a normal ventricular rate is maintained. But often at the time of profound slowing, the auricles fibrillate and, if the drug is then withdrawn altogether, the normal heart action usually becomes reëstablished. I have seen this curious reaction in a number of patients, and it always affords conspicuous relief. The normal rhythm may be maintained indefinitely; in some patients the flutter returns again and requires a repetition of the treatment; in cases which cannot be relieved in this manner, the treatment should be similar to that employed in fibrillation. When relief is obtained, the further treatment of the malady as a whole is that of simple paroxysmal tachycardia.

Auricular Fibrillation.—We know of no remedies which will abolish auricular fibrillation; it is essentially a persistent condition. The treatment is directed mainly to control the rate of the ventricular contractions. Whenever the heart rate exceeds 100 per minute while the patient is at rest, digitalis or an allied drug should be given. It is to its effect on this form of cardiac disorder that digitalis owes its reputation, producing as it does a conspicuous slowing of the pulse rate. It slows the pulse rate in fibrillation as it does in flutter by the production or increase of heart-block, thereby impeding the passage of the rapid impulses from auricle to ventricle. An absolute control of rate is often established and the treatment consists first of all in maintaining the rate at or about normal. In this fashion the increased burden which the heart carries is reduced; with the reduction of rate diastole is lengthened and the heart has more rest. It does not follow that a patient whose auricles are fibrillating should rest in bed; but it is advisable from many points of view that he should lie up while under the influence of digitalis, or at all events until the reaction of the heart to the drug is fully investigated. As a routine, the tincture is given to adults in doses of 10 to 15 minims (0.6 to 1 cc.) three times a day; if the reaction is not noticed within four or five days, the dosage may be increased steadily until symptoms, such as nausea, diarrhœa, headache, or pulse slowing, are observed. As a rule pulse slowing comes first; in other cases it comes simultaneously with other signs of intoxication; if the last have precedence and the ventricular rate remains high for several days, the oral administration of the drug should be discontinued. The dose is reduced as the heart rate falls, and often can be diminished to 5 minims (0.3 cc.) or omitted altogether

while the rate remains normal; not uncommonly, however, the rate begins to rise as the dose is reduced and a fixed dose of larger amount may then be required for long periods. In some few patients large doses alone will maintain a normal ventricular rate; these cases are less favorable. In a few instances the heart rate fails to react; this is seen for the most part in senile cases and when the original rate is not very excessive. It is unwise to maintain the rate at less than 60 or 70 for long; when there is profound slowing the condition may be precarious although the patient is in apparent convalescence. It is during the period of slow action, and especially when, as a result of digitalis, the peculiar coupling of heart beats (Fig. 3) occurs, that unexpected death is encountered. At the height of the reaction strict precautions should be taken against sudden movement or emotional disturbance. It is best to maintain the patient upon pillows and to see that he is fed by hand during the whole of this period, and to employ the utmost care until the heart rate has risen again to normal or until all digitalis has been omitted for several days.

Fig. 3



Venous and radial curves in a case of fibrillation of the auricle, showing the curious coupling of the ventricular beats which occurs under the influence of large doses of digitalis. × ½. It should be noted that while the interval between large and small beats is always constant, the interval between small and large beats is very variable. This is a distinguishing feature in the particular type of coupling associated with fibrillation of the auricle. The venous curve shows the ventricular form of venous pulse.

In patients who are intolerant of digitalis, preparations of strophanthus or squill may be employed, each drug being pushed until a reaction is obtained, when the dose may be reduced. Intolerance to all these drugs is exceptional; in some patients digalen can be used hypodermically or strophanthin may be given intravenously. Strophanthin is also employed in cases of great urgency; the first injection of gr. $\frac{1}{250}$ in a 1 to 10,000 solution of saline is followed by a second and similar dose two hours later. As a rule the two injections suffice to reduce the rate in six or twelve hours, but a third injection of gr. $\frac{1}{250}$ or $\frac{1}{300}$ may be necessary.

The continuous treatment in patients who are up and about is guided by the rate and the urgency of the symptoms. All hearts will not tolerate the same rate of beating; by a judicious employment of digitalis the rate may be maintained so that the burden which the heart carries is not in excess of its capacity. Although patients with fibrillation often return to work, heavy work is not advisable. It should be moderated to meet the circumstances, and if any signs of returning failure appear, namely, increasing pulse rate, easy fatigue or breathlessness, further restrictions must be imposed. All female patients should be warned of the strain of pregnancy.

Belladonna and similar drugs are contra-indicated in fibrillation; they raise the ventricular rate.

As in all cases of disordered heart action, attention should be given to general hygienic measures, and especially to the condition of the mouth and throat.

Slow Action of the Ventricle and Heart-block.—*Simple Bradycardia.*—Slow action of the whole heart requires no treatment, except in the cases in which the retardation produces anemia of the brain or threatens to do so. As a rule bradycardia (rate 50 to 60) is part and parcel of a general condition and the heart is reacting to extraneous influences; it is to the cause, whatever it may be, that treatment is applied in this circumstance. When the bradycardia is of high grade, or when the patient suffers from periodic *standstill* of vagal origin, and where no remediable mischief can be discovered along the course of one or other nerve, atropin or belladonna may be used; this treatment has met with success.

Heart-block.—The treatment of heart-block is regarded from the standpoint of the degree of the block and its duration. Where partial heart-block is of recent origin it is an index of active mischief; the subject of it should lie in bed and be searched thoroughly for the provocative cause. He should remain at rest until all signs of block have vanished or until it is known that the block has become permanent.

Partial heart-block when persistent calls for no immediate treatment; it is to be regarded as one sign of chronic myocardial disease, other signs of which are usually discovered. The patients who show it should be repeatedly examined. Signs of failure, if present, may suggest digitalis medication and the administration of this drug is not contra-indicated, even although it increases the degree of block.

The higher grades of heart-block are usually chronic and stationary and the habits of the patient are governed according to his general fitness or otherwise. Many patients of this class are up and are able to pursue some or all of their usual duties; but usually real bodily activity is impossible or inadvisable. A suspicion of an active or progressive lesion calls for rest and careful observation. Occurring in a syphilitic subject, thorough treatment with mercurials and iodides is indicated.

In those who suffer from convulsions, serious falls during the attacks should be guarded against; many of these patients have lost their lives by falling heavily. There are a number of obvious occupations and sports which are positive dangers to all those who have attacks of unconsciousness. If the convulsions occur successively, it is well to confine the patient over the whole period of the disturbance and for some weeks afterward. Inquiry may reveal predisposing causes of the attacks and these may be remedied; among such causes gastro-intestinal disturbances are common. A few cases are on record in which atropin has seemed to check frequent seizures. But at the time of the convulsions, little can be done as a rule, beyond safeguarding the patient against injury. We know no method of increasing the rate of the ventricle; though a number of drugs, including strychnine, strophanthin, digitalin and amyl nitrite have been given. Adrenalin has been suggested and

seems to offer some prospect of success, though so far as I am aware it has never actually been used.

Premature Contractions.—The presence of premature beats does not suggest a limitation of bodily exercise; it should not be allowed to interfere with the ordinary occupations of the patient. Restrictions are only necessary when associated symptoms or signs render them advisable. The patients may be reassured that such abnormalities are not serious, though the subjects of them may be reëxamined from time to time; reassurance often breeds the desired indifference. Sometimes the provocative cause, excessive smoking, flatulence, constipation, etc., may be identified and removed; but usually the abnormality persists despite precautions and remedies. No drugs seem directly to influence the prevalence of premature beats. The symptoms, sometimes of a distressing kind, may be masked or abolished by bromides given in doses of gr. xv to xxx (1 to 2 gm.) or more a day. The ammonium salt is particularly valuable in tiding nervous patients over periods of exceptional disturbance.

Alternation of the Heart.—The presence of alternation, whatever its associations, is a sign of overtaxation of the muscle. If the heart rate is normal or thereabout, the sign calls for drastic curtailment of work, and of all bodily or mental exertion. In sedentary people it is an indication that the hours of rest should be still further prolonged. It is one of the few signs of heart disease which forbids the administration of a general anesthetic, unless this is imperatively demanded to save life.

Unexpected and Sudden Death in Heart Disease.—When patients who are the subjects of heart disease die suddenly and unexpectedly, it has been our habit to search at the autopsy for evidences of clots, obstructing the pulmonary orifice, one or other auriculoventricular orifice, or a coronary artery; for we know that each of these accidents produces sudden and unexpected death. Yet at the majority of the postmortem examinations after the end has come abruptly, none of these lesions is discovered. It is in the highest degree probable that such patients succumb to a condition termed *fibrillation of the ventricles*, as was first suggested by MacWilliam. Fibrillation in the ventricles or *delirium cordis* is similar to the condition of fibrillation in the auricles; when it comes, coördinate systole in the ventricle is suspended and the muscle exhibits a continuous quivering and ineffectual movement. Its onset spells death. Observation of ventricular fibrillation in the human subject is difficult or impossible for this reason. In animals under experimental conditions, it is of extremely common occurrence; the circulation is immediately brought to a standstill and the animal after a few gasping respirations and twitching movements of asphyxial origin remains permanently quiescent. The experiments of Levy have rendered it highly probable that unexpected death in chloroform anesthesia is of this kind. Fibrillation, be it understood, may appear in a perfectly healthy ventricle; but unhealthy heart muscle is especially prone to fibrillate, as we know from our experience of the auricle; and it is especially in cases of auricular fibrillation or in cases of paroxysmal tachycardia in which auricular fibrillation is also prone to develop, that sudden and

unexpected death is often seen. It occurs most frequently in patients who are under treatment with heavy doses of digitalis or an allied drug. At a stage when improvement is most apparent, when the ventricular action is slow, and when probably the coupled action (Fig. 3) which has been spoken of is present, the catastrophe occurs although convalescence was anticipated. A sudden movement or emotion may precipitate it, perhaps the patient rises in bed to fall immediately; a few gasping respirations, a little twitching of the limbs, rapidly developing cyanosis, and the pulseless patient is still. The postmortem fails to reveal the cause. This picture so closely resembles the outward signs in experiment, the circumstances in which the heart is placed are so suggestive, that it is difficult to remain unconvinced that fibrillation of the ventricles is responsible. Fibrillation of the ventricles is known to be the immediate cause of death when a coronary artery is ligatured; death from embolism of a coronary artery in the human subject almost certainly comes in the same fashion.

Other possible causes of sudden death in heart cases have been mentioned already; vagal inhibition producing a permanent standstill has yet to be proved. The commonest cause of death from ventricular standstill is to be found in heart-block. Of the pathology of unexpected death in angina pectoris and fatty disease of the heart, we have little or no knowledge. Sudden death is not uncommon in those who establish alternation of the heart; in this condition, too, we do not know the manner in which the heart fails.

The following general treatises are mentioned for reference:

Wenckebach, *Arhythmia of the Heart*, translated by Snowball, Edinburgh and London, 1904

Mackenzie, *Diseases of the Heart*, London, 1910.

Kraus and Nicolai, *Das Electrokardiogramm*, Berlin, 1910.

Lewis, *Mechanism of the Heart Beat*, London, 1911; *Clinical Disorders of the Heart Beat*, London, 1912; *Clinical Electrocardiography*, London, 1913.

CHAPTER IV.

DISEASES OF THE MYOCARDIUM.

By ROBERT H. BABCOCK, M.D., LL.D.

DISEASES RESULTING FROM DERANGEMENTS OF CARDIAC NUTRITION.

Both the functional and structural integrity of the heart muscle is dependent upon a supply of healthy blood, any abnormality of which in either the constitution or amount must affect it more or less seriously. In simple anemia the heart may display weakness, dilatation, and increased frequency, whereas in pernicious anemia it may suffer degeneration. Again, intestinal intoxication may be responsible for disturbed rhythm, while the toxins of acute specific fevers are capable of producing structural changes of a most disastrous kind. It is, however, the mechanical interference with its blood supply from coronary sclerosis which is the most surely injurious, and it is the myocardial disease of this origin that is most frequently encountered. Accordingly, whenever there is a structural defect with insufficiency of the myocardium, it is usually found to depend upon a disorder of cardiac nutrition.

Etiology.—Acute Myocardial Degeneration.—*Acute Infections.*—For the most part it is the parenchymatous form of acute myocarditis which is seen as a result of acute infectious diseases. It is a manifestation of the action of toxins conveyed to the myocardium in the blood, and hence the likelihood of degeneration is proportionate to the intensity of the toxemia and not its continuance (Romberg). Of the infections likely to lead to myocardial degeneration the most prominent are *diphtheria, typhus,* and *typhoid fever.* The involvement may declare itself during the course of the fever, but in many instances it becomes apparent only after the subsidence of the primary disease.

Rheumatic fever, scarlatina, variola, and *influenza* are also capable of producing this form of acute degeneration. In the case of rheumatic fever, it is often the involvement of the myocardium rather than the endocarditis or pericarditis which renders the heart symptoms so serious. The injurious influence of *influenza* upon the heart muscle is a matter of every-day observation. Not only is the function of the organ disturbed in the course of the influenza, but signs of cardiac inadequacy may develop a considerable time after. The danger to life from such a degenerative process makes prolonged observation of the patient after convalescence from an attack of influenza highly important. *Gonorrhœa* is also to be enumerated among the specific infections which may occasionally be responsible for an acute myocarditis (Romberg).

Toxemia of Pregnancy.—Parenchymatous degeneration of the myocardium is a not infrequent postmortem finding in women who have

died during an attack of eclampsia. The lesion may vary from cloudy swelling to pronounced fatty degeneration. It is believed also that this condition of the heart muscle is responsible for the symptoms of cardiac insufficiency observed in pregnant women suffering from toxemia, yet without convulsions. Bacon states that the symptoms of this form of myocarditis occur in about 1 per cent. of pregnant women, a proportion greater than the percentage of convulsions.

Emboli.—Plugging of a coronary artery is a cause of acute degeneration and inflammation of the myocardium. If it is benign, the result is an area of acute necrosis, but if the emboli are of a septic nature, abscesses result. Such septic infarcts may occur in the heart walls as a result of suppurative processes in remote parts, but are most common with infective endocarditis.

Pyemia also predisposes to septic myocarditis, and hence it was that gladiators in the time of Galen were frequently found to have this form of acute myocarditis. The better surgical methods of today have rendered pyemia comparatively rare, and hence abscesses of the myocardium are infrequent unless in the course of puerperal endometritis or septic endocarditis.

Coronary Thrombosis.—The enumeration of the causes of acute myocardial degeneration would not be complete without mention of coronary occlusion in consequence of thrombosis. A coronary artery may become gradually thrombosed, in which event the nutrition of the heart suffers with corresponding slowness, but when the blood supply to an area is suddenly shut off, degeneration follows rapidly, or, in other words, acute necrosis results. Thus are provided the conditions which favor rupture, and hence the extreme gravity of coronary thrombosis.

Chronic Myocardial Degeneration.—1. *Intrinsic Causes.*—The conditions which predispose to slow decay of the heart muscle are many and varied. Some of them are clearly understood and plainly apparent, while others are indefinite and difficult of satisfactory explanation. Belonging to the former class are all those factors which reside in the heart itself and hence may be called intrinsic. In the second are most if not all of the conditions which, existing outside of the organ, may be called extrinsic and which for the most part are really responsible for the intrinsic causes.

Coronary Sclerosis.—This is undoubtedly the one great intrinsic factor to which chronic changes of the myocardium are to be attributed. The sclerosis produces its effect on the heart muscle by its interference with the adequate supply of blood, not by the conveyance of toxins, although these may, in large part at least, be responsible for the sclerosis. The influence of coronary disease over the nutrition of the heart stands in direct relation to the degree of sclerosis and the rapidity of its development. Thus, if the lumen of the arteries be gradually narrowed, the result is the development of fibrosis or fatty degeneration according to the degree of the coronary narrowing. If, on the contrary, a thickened and narrowed branch suffers sudden thrombosis, the result is acute softening of the part supplied by that branch. Since a terminal twig possesses but a small caliber it may require comparatively slight thicken-

ing of its coats to induce thrombosis, and hence the frequency with which areas of necrosis are found in association with changes of a chronic nature in other parts.

Cases are now and then met with in which, despite pronounced changes in the coronaries, the integrity of the myocardium does not appear to have been seriously affected. In them either the arteries were still capable of conveying sufficient blood for the needs of the muscle, or the vessels of Thebesius were able to carry enough blood into the myocardium to prevent disastrous loss of its nutrition.

In certain cases of the so-called senile heart, one is often astounded to find at autopsy such extensive and pronounced degeneration as to make him wonder how the organ managed to perform its function without clinical signs of greater inadequacy than actually existed. The explanation can only be found in the failure of the degeneration to involve the conducting fibres, or in the absence of other intrinsic factors, which, if present, would surely have served to overpower the organ.

Valvular Lesions.—These bring about degenerative changes in the myocardium in the course of time. Their mode of action is probably manifold, but the main factors are perversions of cardiac metabolism and increased work. Disturbance of the heart's nutrition results from lack of healthy blood on the one hand and defective removal of waste products on the other. Accordingly, all forms of valvular disease do not prove equally disastrous in their effects upon the heart walls. Aortic and mitral stenosis, especially the former, diminish the supply of blood sent into the coronaries because they lessen the amount discharged into the aorta; but in addition, mitral obstruction, through the stasis which it induces in the right heart, interferes with free flow from the coronary veins. Consequently it is in this form of valve disease that we meet with pronounced degrees of *brown atrophy.*

Regurgitant lesions in the left side of the heart also occasion myocardial degeneration in a similar manner, but as they would not appear to interfere so seriously with cardiac nutrition, at least in their earlier stages, they seem to exert their effect largely through the increased strain on the heart walls. This is particularly true of aortic insufficiency and hence it is in this affection that we sometimes see pronounced fatty degeneration of the enormously hypertrophied left ventricle.

The ventricle is called on for great increase of work, and at the same time demands increased nutriment both to maintain its nutrition *in statu quo* and to enable it to perform the extra work. If factors incident to its hypertrophy and dilatation prevent its receiving an adequate blood supply, then in time its fibres will undergo fatty degeneration. But, however the degenerative changes in chronic valvular disease may be explained, they certainly are of greater importance in bringing about the final break in compensation than is generally recognized.

Heart Strain.—This may result from conditions incident to the manner of life and hence to be classed under the head of extrinsic causes, but the kind of strain here referred to is that due to conditions residing in the heart itself. As suggested in the preceding paragraph, lesions of the valves tend to myocardial decay because of the strain to which they

subject the cardiac muscle, but there are other intrinsic causes independent of valvular disease. The healthy heart is capable of enduring an enormous amount of work without injury so long as its nutrition is maintained. But when in consequence of dilatation, however caused, the efficiency of the organ is reduced, degeneration is bound to ensue in time. Not only does the stretching of its walls augment its work by reason of the greater amount of residual blood left after each systole, but because of its enfeebled contractions a diminished supply of blood is sent into the aorta and coronaries. The nutrition of the myocardium suffers consequently and degenerative changes result even though the coronary arteries be intact. It is probable that the hypertrophied heart secondary to prolonged high blood pressure with or without serious kidney changes can sustain the demands made upon it so long as its supply of blood meets its requirements, but when this becomes inadequate from any cause, then to heart strain is added degeneration, and myocardial incompetence soon declares itself. From the foregoing it is plain that heart strain as a factor in the production of chronic myocardial decay stands in close relation to and cannot be separated from nutritive disturbance and very likely also various infective agencies.

2. *Extrinsic Causes.*—Some of these are manifestly extraneous while others are so intimately associated with the intrinsic factors as to make their separation difficult. These latter will be next considered.

Mode of Life.—This includes a great variety of influences of which some appear to involve heart strain, while others are pernicious through toxic or nutritional effects. But under this head are embraced factors referable to business, social, dietetic, psychical, and other influences. In this class of cases, therefore, come instances of what Fraentzel termed Idiopathic Enlargement of the Heart. They are usually associated with hypertension in persons of both sexes who for years have led a strenuous life with insufficient recreation and exercise. Some are tireless men of affairs who lead a too sedentary existence and perhaps whip up their flagging energies with stimulants and excessive protein diet. Others may be less strenuous but they are also too disinclined to physical exercise and habitually eat and drink more than they require. Accordingly they present instances of Fraentzel's Luxus Consumption which leads to abdominal corpulence, chronic nephritis, and abnormally high blood pressure. Even when, as in some cases, blood pressure is not excessive, it is probable that the intra-abdominal vessels, on which undue strain falls, have already begun to suffer sclerotic change.

In still other individuals general corpulence develops and eventually subjects the myocardium to degeneration from chronic overwork or fatty overgrowth. But in whatever manner may be explained the gradual injury the heart muscle is suffering it is explicable by the mode of life rather than any toxic or intrinsic factors. At all events we frequently see cases of myocardial incompetence and presumable degeneration in busy, strenuous men and women who give no history of any other etiological factors than their injudicious manner of overstoking and overdriving their bodily machinery.

Still another cause on which German writers, as Romberg, lay stress

are neuroses, in particular neurasthenia and hysteria. The explanation is that owing to their extreme excitability and emotional instability they subject their cardiovascular system to sudden and violent strain, as in tachycardia from fear, anger, worry, etc. Such no doubt may be the explanation in some persons, but underlying some of these neuroses are factors such as chronic focal infections or previous acute illnesses.

Excessive Physical Toil and Hardships.—Considerable importance in the production of myocardial disease is attached to the severe physical exertion, together with the exposure and privations, experienced by soldiers, sailors, mountaineers, day laborers, coal miners, etc. Doubtless, the element of strain and malnutrition of the heart muscle comes into play in such individuals, but one cannot ignore the influence of other factors, such as hard drink, irregular habits, and syphilis.

Alcohol.—This is a subject about which much conflict of views still exists. The most recent experiments and pathological studies seem to prove that the directly injurious effect of alcohol is felt not by the cardiovascular system but by the stomach and liver. It is asserted that postmortem examination of drunkards fails to reveal sclerosis of the arteries and associated degeneration of the heart muscle. On the other hand older writers point to the fatty degeneration of the myocardium found in inebriates. To the present writer it would seem that if such changes are found in persons dead of chronic alcoholism they are to be attributed not to the alcohol *per se* but to other factors intimately connected with the abuse of strong drink.

Immoderate beer drinking, as in Bavaria, is held by German clinicians to produce disease of the heart muscle, though not so much by reason of the alcohol as by the cardiovascular strain incident to the absorption and elimination of many liters daily. Rosenbach and Krehl also attribute no inconsiderable etiological influence to the obesity caused by the relatively large amount of nutriment contained in the beer.

Syphilis.—Warthin has shown that the *Spirochæta pallida* displays a predilection for the tissues of the cardiovascular system as well as the nervous system. In both congenital and acquired lues, areas of fatty degeneration may be found in the myocardium, and Warthin believes that syphilis is the cause of this form of chronic myocardial degeneration far oftener than hitherto believed. It would be well therefore for the physician to sift to the bottom the possibility of syphilitic infection in all cases of cardiac inadequacy for which other obvious etiological factors cannot be held responsible. To this end a reliably performed Wassermann test is often of the greatest service.

Chronic Focal Infections.—It is now well established that acute infections such as typhoid fever, influenza, and pneumonia may and often do set up changes in the walls of the bloodvessels and heart which in after years declare themselves as a slowly progressive degenerative process. So, also, a chronic infection like pulmonary tuberculosis can be responsible for coronary sclerosis and fatty degeneration of the myocardium. It does not seem unreasonable to assume therefore that a chronic focal infection is capable of inducing degenerative changes in both bloodvessels and heart muscle. Cases have been reported of

serious myocardial incompetence due apparently to no other cause than a chronic cholecystitis either with or without gall-stones. In some of these instances the peripheral arteries were manifestly thickened and stiff and the behavior of the heart was such as to leave no room for doubt as its being seriously degenerated. In some of these cases it may be that the typhoid fever many years earlier initiated the process, but in others it seemed a fair assumption that the chronic gall-bladder infection led to the myocardial degeneration and dilatation, either through prolonged though slight cholemia or possibly by irritation of the splanchnic and consequent increase of blood pressure, since recent experiments appear to show that splanchnic irritation raises the amount of epinephrin contained in the renal vein.

Chronic *appendicitis* as well as prolonged pus-tube infection can disturb cardiac action seriously and in time bring about altered rhythm and dilatation, with interference with cardiac nutrition and degeneration.

Hyperthyroidism, although not properly a focal infection in the sense here meant, yet may be appropriately mentioned in this connection since the cardiac disorder it induces is capable of causing dilatation and degeneration of a most serious nature. Chronic *tonsillar abscess* has been known to induce symptoms of chronic nephritis, and why may it not likewise be capable of leading to serious changes in the myocardium? At all events we are but lately coming to recognize the disastrous effects that may follow prolonged focal infections, and it is not going afield to assume that their malign influence may be expended on the myocardium as well as on other structures.

Drugs.—It has long been recognized that fatty degeneration of the heart may result from phosphorus poisoning and the prolonged use of arsenic.

Exhausting Diseases.—Cancer, chronic dysentery, or other exhausting discharges, pernicious and even severe secondary anemia, chronic suppurating diseases, all lead to myocardial degeneration. In pernicious anemia the most extreme grade of fatty degeneration is often met with, while in protracted suppuration either this same form or amyloid change in the heart muscle may be found.

Morbid Anatomy.—Acute Changes in the Myocardium.—(*a*) *Acute Parenchymatous Degeneration.*—This condition is often spoken of as acute myocarditis, a term etymologically incorrect, since it implies an inflammatory and not a degenerative process. The condition results from the action of the toxins of acute infections. It is a diffuse process, characterized by cloudy swelling and granular degeneration of the muscle fibres. The myocardium looks pale and opaque, and is soft, flabby, and easily torn. Microscopically the fibres are seen to be swollen, their protoplasm more or less granular, and their striations are indistinct.

(*b*) *Acute Interstitial Myocarditis.*—This occurs in two forms, purulent or simple, depending upon the cause. The former is the result of septic emboli, while the latter occurs in certain infectious diseases, *e. g.*, diphtheria, and typhoid fever, and in connection with acute pericarditis.

Purulent myocarditis is characterized by septic infarcts of variable number and extent. Occasionally these abscesses rupture into the

endocardium or pericardium. These foci of suppuration are usually multiple and vary in size from that of a pin's head to that of a pea. They appear as whitish or grayish areas which on section are depressed below the plane of the cut. Fluid or semifluid pus may be found in the larger abscesses, while the smaller are seen microscopically to consist of masses of polymorphonuclear leukocytes surrounded by a zone of degenerating muscle fibres. Bacteria may often be demonstrated in these areas.

The simple form is very rare and is characterized by infiltration of the tissue with lymphoid and plasma cells. There is also considerable degeneration of the muscle fibres shown by swelling and destruction of their nuclei. Foci of such changes are more numerous in the wall of the left than of the right ventricle, and are generally situated close beneath the endocardium.

(*c*) *Acute Necrosis.*—This is a form of acute parenchymatous degeneration which results from sudden occlusion of a coronary artery by thrombosis or non-septic embolism. It is variously designated anemic necrosis, white infarct, acute softening, and myomalacia cordis. The degeneration is circumscribed and is most often found in that portion of the left ventricle and septum supplied by the anterior coronary artery.

The affected area has a yellowish-white or grayish-red color, is of an irregular wedge shape, and projects slightly above the surrounding level. The abrupt shutting off of the blood supply to the area leads to coagulation necrosis, which is soon followed by an inflammatory infiltration of the part. Ultimately this necrotic patch becomes transformed into a zone of scar tissue.

Chronic Changes in the Myocardium.—(*a*) *Fibrosis, chronic interstitial myocarditis, fibroid degeneration,* are terms used to designate a condition in which the muscle fibres are replaced by fibrous tissue. The process may be diffuse, but is more often circumscribed. In the diffuse form there is a progressive atrophy of the muscle fibres with a corresponding increase of the interstitial connective tissue. When not very pronounced the condition is usually associated with a thickening or hypertrophy of the muscle wall. To the unaided eye the myocardium may, in the slighter degrees, look healthy, but when the fibrosis has led to thinning and dilatation, the heart is apt to have a paler appearance than normal and to cut with resistance.

In the circumscribed form there are smaller or larger areas of fibrosis, which in reality is a manifestation of nature's attempt to conserve the myocardium against the injury wrought by some antecedent process. Thus it may be the final or reparative stage of an acute degenerative change, as anemic necrosis. The area becomes invaded by young connective-tissue elements which at length are converted into a firm fibroid cicatrix. The extent of such a focus is determined by that of the original lesion, but in most cases is not very great.

Foci of fibroid degeneration are most commonly found in the wall of the left ventricle not far from its apex, in the upper two-thirds of its posterior portion in proximity to the auricles, in the papillary muscles of the left ventricle, and in the interventricular septum. When not

very extensive or not disturbing cardiac rhythm they may not seriously interfere with the functional integrity of the heart, but in some instances they lead to localized dilatation.

(*b*) *Aneurism of the Heart.*—Under this term is designated, not that bulging of the semilunar valves sometimes seen as a result of endocarditis, but a circumscribed thinning and dilatation of the wall resulting from fibroid degeneration. The condition is usually single but may be multiple. The pouching occurs most often at or near the apex of the left ventricle, since here is the most frequent seat of fibrosis. The aneurism may be of such small size as to scarcely merit the term, or it may be so extensive as to constitute a sac of the size of the ventricle or of the heart itself. The pouch is very apt to be occupied by a thrombus, especially when it communicates with the cavity of the ventricle by a narrow opening. The formation of a coagulum within the sac is then conservative, as it tends to prevent rupture. In the majority the wall of the aneurism is unequal to the pressure of blood within it, and rupture takes place.

(*c*) *Fatty Degeneration.*—In this form of chronic myocarditis the heart muscle presents a generally pale appearance, with patches and streaks of yellowish-brown color, on which account it has been compared to a faded leaf or a tabby cat. The organ is much softer than normal, and can be easily penetrated by the finger. The areas of fatty degeneration are most common in the wall of the left ventricle near its apex, next in that of the right ventricle, in the interventricular septum, and in the wall of the right and left auricle in the order mentioned. The muscle close beneath the endocardium is affected by this form of degeneration more than that underneath the pericardium, and the brownish or yellowish area may sometimes be plainly seen from within the heart cavities. Microscopically the protoplasm of the fibres is found replaced by fat-drops arranged in rows and situated at the junction of the transverse and longitudinal striations.

(*d*) *Rupture of the Heart.*—Fortunately this accident is rare, and yet it occurs with sufficient frequency to make its recognition important as a cause of sudden death. The conditions predisposing to rupture are fatty degeneration and areas of acute necrosis, a focus of suppurative myocarditis, extreme fatty infiltration, and even a gumma of the myocardium. Fatal hemorrhage into the pericardium has been known to follow rupture of a minute coronary aneurism. Rupture of the heart muscle takes place most commonly on the wall of the left ventricle near the septum, but may be situated in any portion of the organ which has undergone serious degenerative change.

(*e*) *Fatty Heart.*—This term is used to designate the fatty degeneration described above or an excess of adipose tissue. In well-marked cases of the latter kind there is an overgrowth of subepicardial fat which may cover the heart like a blanket and completely conceal the muscle beneath. It is the *cor adiposum* of old writers. There is also an infiltration of fat between the muscle fibres which in places have become atrophied or may be the seat of fatty degeneration. In extreme instances the heart is relaxed and its cavities are dilated. This increase of the adipose tissue of the organ is often combined with general obesity.

When a heart is the subject of chronic myocarditis, it is very apt to present a picture made up of these varying conditions—fibrosis, fatty degeneration, and fatty overgrowth. As these changes depend upon disturbances in the nutrition of the myocardium, more or less evidence of coronary sclerosis is generally found. If there are associated changes in the kidneys and general arterial system, the heart is likely to be hypertrophied and dilated. In cases in which the sclerosis is most marked in or limited to the coronary arteries, the organ may be markedly atrophied and the myocardium really furnish a good picture of brown atrophy. This is seen especially in the so-called senile heart.

(*f*) *Fragmentation and Segmentation of the Myocardium.*—This condition, first described by French writers, has received much study by pathologists in Europe and America. Fragmentation is so called because the fibres are found fractured, the cells being broken at the level of the nuclei. In segmentation there is a separation of the fibres in their cement substance. The two conditions may be combined in the same specimen. This change in the myocardium may occur in the death agony or it may occur before dissolution, and prove a clinical and pathological entity of importance, although very difficult, if not impossible, of recognition during life.

Other Rare Forms of Degeneration.—(*a*) *Amyloid Degeneration.*—This is sometimes met with in the same class of cases as is this change in other organs. It occurs in the interstitial connective tissue and in the coats of the bloodvessels, but not in the muscle fibres.

(*b*) *Hyaline Transformation.*—This may occasionally be seen after protracted fevers. The fibres are swollen, homogeneous, translucent, and have nearly or quite lost their striations.

(*c*) Lastly, the muscle fibres may become infiltrated with lime salts and be the seat of *calcareous degeneration,* which is very uncommon.

Symptoms.—Acute Parenchymatous Myocarditis.—These depend on the nature and extent of the myocardial change. It may not declare itself by clinical signs and may only be recognized postmortem, or the disease is not suspected until the sudden death of the individual declares its existence. In other cases there are symptoms sufficiently pronounced to permit of their correct interpretation by the attentive physician, while in still another set of cases the symptoms due to the myocarditis are obscured by and very likely referred to some associated and easily recognized affection of the heart, as endocarditis or pericarditis.

Acute myocarditis seems to be especially dreaded and looked for by physicians in the course of *diphtheria,* but according to Romberg and Schmaltz its symptoms occur in only from 10 to 20 per cent. of cases. When, however, symptoms so arise they are likely to be most serious. It should be remembered that they may appear at any time from the close of the first to that of the fifth or sixth week, though most often in the second or third after the commencement of the illness.

Examination of the heart at this time is likely to disclose great feebleness or even absence of cardiac impulse, increase of relative dulness transversely, and marked weakness of the tones. The first sound at the apex may be muffled and toneless, or it may be audible as a short, val-

vular tone which is accompanied by a more or less faint, blowing, systolic murmur. This murmur is generally restricted to the mitral area and denotes not an associated endocarditis necessarily, but a so-called muscular mitral insufficiency.

This form of mitral incompetence is due to defective action of those various factors which normally produce effective closure of the mitral valve. In reality, therefore, it is a dilatation bruit which is heard, and hence it may wholly disappear after the cardiac asthenia has been recovered from and the left ventricle has returned to its normal size.

Signs of stasis are not so pronounced in the liver and other viscera as to attract special notice, and save for the pallor or the cyanosis the patient may not to the inexperienced observer, betray by his appearance the serious state of his circulatory apparatus. On this account cases of grave asystolism are occasionally overlooked, and children convalescing from diphtheria are permitted to play about before the heart is equal to the exertion. It is probable that if the heart had been critically examined in the unexpectedly fatal cases it would have displayed some features indicative of left-ventricle weakness and dilatation.

In typhoid fever acute parenchymatous myocarditis may be shown by emptiness and compressibility of the pulse rather than by marked frequency. The pulse rate is characteristically slow in proportion to the pyrexia and general feebleness. In those cases in which myocarditis seemed to the writer to exist, greater rapidity of the heart's action was noted than is usual in typhoid fever, yet not so great as might have been expected in grave cardiac asthenia. The first sound at the apex is likely to be strikingly wanting in clearness and strength, although an actual murmur may not be detected. Careful percussion may determine an increase in the area of dulness out of proportion to the clinical evidence of myocardial inadequacy. The objective manifestations of the myocarditis are to be sought, therefore, in the characters of the pulse and in the auscultatory findings rather than in venous stasis.

Influenza is another infection prone to exhibit signs of myocardial weakness from acute parenchymatous degeneration. The pulse is accelerated and feeble, while the heart tones are correspondingly deficient in strength. These symptoms may appear during the primary affection or be first noticed after the individual has resumed his activities. During the acme of the illness the weakness and rapidity of the pulse are apt to be attributed to the fever and prostration. But upon the patient returning to work he is found to be a little short of breath and easily fatigued. There may be a slight or vague sense of discomfort in the precordium rather than of positive pain, and now and then there may be palpitation or vertigo. The color of the face is ashen or faintly cyanotic and on examination the heart's action is found rapid, perhaps irregular and intermittent. The pulse is of low tension and the apex beat is indistinct or displaced somewhat to the left. The tones are weak, especially the mitral first sound, which is apt to be accompanied though not obscured by a soft bruit. Comparison of the pulse rate and systolic blood pressure before and after exercise generally discloses more or less pronounced evidence of defective myocardial response.

Under rest in bed and appropriate treatment some of these patients recover their health and the heart no longer exhibits signs of inadequacy. In other cases the acute seems to pass into a chronic myocarditis, and the pulse never regains its former regularity and strength. The heart is permanently enlarged and there may be a permanent apex murmur.

In *rheumatic fever* the parenchymatous degeneration of the cardiac muscle is very apt to be masked by the signs and symptoms of an associated injury of the endocardium. When an acute endocarditis appears in children there is generally pronounced dilatation of the chambers most nearly concerned. We are wont to refer such enlargement of the heart to mechanical causes, but it is probable that pronounced dilatation does not occur unless acute myocarditis also exists. If the heart muscle is not seriously affected in its nutrition, a valvulitis is speedily compensated for by the development of hypertrophy in that division of the organ which has to bear the brunt of the strain. Therefore, when in rheumatic fever a degree of dilatation and asystolism develops which is disproportionate to the apparent endocardial mischief, acute parenchymatous myocarditis may be assumed.

If the heart walls are extensively damaged the rhythm of the contractions is likely to be disturbed. The pulse is apt to be accelerated rather than retarded, and to display more or less irregularity in time, force, and volume. Greater perturbation of the heart's action results from comparatively trivial exertion or mental excitation than should be the case. The patient becomes noticeably pale and may have an anxious look, yet questioned as to pain he denies this altogether or speaks of a dull, oppressive feeling at the heart rather than acute distress.

If such patients recover at all, it is only after weary months of scarcely appreciable improvement. Not only has the nutrition of the myocardium been affected, but that of the organism in general has been seriously compromised. In particular it is the kidneys which in these acute infections are likely to share in the inflammatory process. This nephritis disappears long before the myocardium acquires sufficient hypertrophy to denote a compensatory reëstablishment of its power. Even then, after the individual has returned to his previous manner of life, more or less arhythmia is likely to persist.

Acute Interstitial Myocarditis.—Cardiac symptoms are very likely to be masked by those of the underlying condition. When, however, the myocardial inflammation dominates the scene, the clinical picture is very like that of malignant endocarditis. There may be slight rigors, an intermittent pyrexia, and enlargement of the spleen. The heart's action is rapid and feeble and the area of cardiac dulness may be increased. The sounds are apt to be clear but weak, and murmurs are wanting. In some cases there may be nothing to indicate the critical state of the myocardium and the condition is recognized only at autopsy. In some of these cases the existence of the suppurative myocarditis is first revealed by the symptoms of collapse, the heart wall having ruptured into the pericardium. If an abscess has broken through and discharged its contents into the blood stream, there are the phenomena of septic infarcts in distant parts, skin, kidney, spleen, liver or brain.

When viewed from the standpoint of symptomatology, acute myocarditis of either form may be divided into 2 classes: (1) cases in which symptoms pertaining directly to the heart are either absent or so obscure as to be overlooked; and (2) cases in which evidence of cardiac incompetence is too conspicuous to be overlooked or may be discovered if sought for. For the most part it is the first class of cases which are especially dangerous and for the discovery of which the physician should be always on the lookout when treating any case of acute infection. He must not be deceived by the want of obvious signs of venous stasis, for these are more apt to be absent than present. The reason for this is conjectural. It may be due to toxic paresis of the vasomotor centres as suggested by Romberg, or under the influence of a splanchnic neuritis (Veronese) there may be stasis within the great veins of the abdomen with corresponding emptiness of the superficial veins. The physician should also be on the watch for slight yet significant signs of myocardial weakness, such as feebleness and emptiness of the pulse rather than marked frequency; perturbations of rate and rhythm out of proportion to the degree of effort that evoked them; sudden and alarming periods of weakness when the pulse grows rapid and almost imperceptible; listlessness and weakness on the part of the patient and apathy or marked restlessness. Striking pallor of the countenance, vomiting, and precordial pain are symptoms which, if not always present, are yet very significant and should excite apprehension. If combined with some of the evidences of myocardial incompetence described, they render the existence of acute myocarditis highly probable.

The *course* may be quite diverse both as regards onset and duration. It may set in suddenly and under symptoms of ever-increasing severity lead to death in a few days or weeks. On the other hand, the myocarditis may develop insidiously and remain latent up to the moment of unexpected death; or there may be periods of entire absence of symptoms which alternate with times of alarming asystolism and all the appearances of impending dissolution. Lastly, the affection may first declare itself by signs of cardiac inadequacy of greater or less severity, several weeks after all thought of danger has passed.

Chronic Myocarditis.—There is much diversity in detail presented by the clinical picture of chronic myocardial degeneration, yet different as these points of contrast may be, the background remains ever the same, namely, cardiac incompetence. The differences are determined by the seat and extent of the morbid anatomical changes as well as by their exact character and their association with degenerative changes in other organs. Cases falling under this head may be variously classified according to their pathogenesis, their pathological peculiarities, or their clinical manifestations. An etiological grouping would be very desirable, but seems impracticable in the present state of our knowledge, since we are not able to decide which of several factors may be the essential one. A classification based upon the precise nature of the myocardial change is likewise, not feasible since various changes generally exist in each case. We are confined, therefore, to a division of cases based on their clinical manifestations.

Two main groups of cases may be distinguished: (1) those in which symptoms referable to the heart are latent or so disguised as to escape recognition, and the existence of heart disease is first declared by sudden death; (2) those in which symptoms of cardiac inadequacy are more or less conspicuous. The cases making up this second group may be subdivided according as symptoms are distinctly cardiac or are blended with others attributable to disease of other structures than the myocardium. In reality it is the union of several such interdependent conditions which accounts for the diversity in the details of the clinical picture. Accordingly, this arrangement of cases will be maintained so far as is compatible with clearness and accuracy.

Latent Cases.—In this group belong the occasional instances of sudden and unexpected death occurring among middle-aged or elderly and apparently robust men. They are very apt to be reported as cases of apoplexy, but are in reality instances of cardiac paralysis or sudden heart failure. The Germans call it "herzschlag" (heart stroke), and appear to recognize its exact nature more often than is done in this country. In instances of this kind it may be that a man engaged in conversation or perhaps at the end of a meal, in whom nothing abnormal has been noted, falls over dead. In the press reports of these cases it is generally said that the deceased was in excellent health and had experienced no symptoms that indicated to his friends the existence of heart disease. Such is doubtless true in many instances. In others there have been symptoms which were attributed to indigestion, nothing more. It is quite likely, nevertheless, that if these victims had been critically examined they would have exhibited to the skilled observer some of the signs which point to the probability of chronic myocarditis.

The reasons for the latency of these cases are to be found in the insidiousness of the changes going on in the heart muscle and in the location of these changes. Their seat may be such as to cause a perpetually irregular pulse or to interfere with the conducting fibres and lead to heart-block. Even though this latter may not occur, perpetual arhythmia inevitably brings about dangerous heart weakness.

On the other hand, there may be a condition of hypertrophy with dilatation of the left ventricle, the former condition having predominated for years and thus precluded subjective symptoms. The degenerative process slowly and insidiously saps the strength of this hypertrophied wall, and at length it becomes incapable of withstanding high intraventricular blood pressure. So at length comes a moment when under the inhibitory stimulus of some strong emotion, an unwonted or hasty physical effort, a hearty meal, etc., blood pressure within the degenerated ventricle is raised to an unsupportable degree and the heart stops in diastole. Such a time of danger may arise in the life of any person whose myocardium has become degenerated.

Examination of the heart in these latent cases would probably reveal signs of general cardiac hypertrophy. Although by reason of the capaciousness of the chest the area of heart dulness may appear natural, still the increase of pulse tension and the slight thickening of the

arterial coats evince the strain on the heart, while the intensity and ringing quality of the aortic second tone bear confirmatory testimony.

In these cases there is more or less acceleration of the pulse, or a slight amount of breathlessness on exertion to which the individual pays no heed, having attributed it to his increasing weight or age and, therefore, supposed it quite natural. On brisk exercise also systolic blood pressure does not rise and remain up as it should after the pulse has fallen to its former rate. Such, at all events, are the evidences of incipient, cardiac incompetence which may be detected in men who considered themselves in perfect health.

Cases with High Blood Pressure and General Cardiac Hypertrophy.—It must not be supposed that the cases grouped under this head monopolize these features of the pulse and heart. They only constitute the findings which stand forth most conspicuously in the examination of these cases. Fraentzel designated them idiopathic enlargement of the heart to distinguish them from instances of hypertrophy secondary to chronic valvular disease. In the writer's experience they are most commonly found among the large-framed, energetic men who were described under Etiology as engaged in office work and, under the influence of good living, early develop a degree of abdominal corpulence which puts an injurious burden upon their circulatory apparatus.

Slowly and insidiously the myocardium has been answering to the heavy demands made upon it by ever-increasing thickness of its walls, not a true hypertrophy of its muscular elements, but a false hypertrophy in consequence of the growth of connective tissue. To whatever special factors the augmentation of blood pressure is to be ascribed, the fact remains that for an indefinite time there has been high and sustained pulse tension. There may or may not be demonstrable thickening of the arterial coats, and some degree of renal change may be shown by urine containing a few granular and possibly hyaline casts. Now and then a trace of albumin may be detected, but on the whole the renal elimination is satisfactory.

Year by year the elevation of blood pressure becomes more pronounced, and little by little the development of fibrous tissue undermines the resisting power of the myocardium. At length symptoms begin to declare the strain to which the heart is slowly yielding. In some cases it is *dizziness* which first attracts attention. The sensation is slight and transient, perchance, but it occasions uneasiness, and a physician being consulted, the state of the heart and vascular system is recognized. Measures are prescribed for reduction of pulse tension and the patient is relieved of his annoying vertigo. In some instances the excessive blood pressure leads to a severe and almost uncontrollable attack of epistaxis, and thereafter symptoms are relieved for a time.

In other cases it is *breathlessness on exertion* which is first noticed. This, too, may be lessened or removed for a time, but, as a rule, it does not vanish altogether. Associated with the shortness of breath may be a sensation of weight or *fulness in the precordium*, or there may be a dull ache or pain in the upper cardiac region whenever the man walks at more than a very moderate pace.

In still other cases the initial symptom which takes the patient to a physician is *palpitation*. It is often described as a thumping or pounding of the heart which attracts notice during exertion or at night. In some instances the individual is unable to lie on his left side because of this sensation. Not infrequently breathlessness is experienced as well as palpitation or vertigo. In other cases the patient complains of unwonted weakness or of *epigastric fulness* or pain which he attributes to indigestion. His conviction of its being only a digestive disorder is increased by eructations or by aggravation of his sensations after meals. If he is a little short of breath, especially after eating, he regards it as due to bloating with wind.

In some one of these various ways this type of myocardial incompetence first makes its advent known. As time goes on the degree of cardiac inadequacy increases and the individual finds himself attending to his ordinary duties with ever-growing difficulty. Usually at this time it is the shortness of breath which incapacitates him. He is aware of decreasing strength and endurance, but it is the dyspnœa which really torments him. He is noticeably short of breath even when at rest in his chair, but it is when he walks about or when he goes to bed at night that he suffers the most. Things go on from bad to worse and at last he gives up and stays at home.

Examination of the heart now discloses plain signs of myocardial incompetence. The pulse is more or less accelerated, usually regular, and of high tension. The palpating finger finds it difficult to compress the artery and the sphygmomanometer registers anywhere from 160 to 200 mm. Hg., or in exceptional instances even higher. The radial arteries roll under the finger but are not generally markedly sclerotic. There may not be pitting, or even puffiness, of the ankles.

The apex beat if perceptible is found in the fifth or sixth intercostal space, outside the nipple line, and by measurement from four to five inches to the left of the median line. There may be epigastric pulsation of variable strength according to circumstances. Deep-seated and superficial dulness is increased in all directions but chiefly to the left, and the outline is quadrangular, indicating general enlargement. The heart sounds are somewhat enfeebled, especially the mitral first, which is often accompanied by a blowing murmur. The pulmonic second tone is likely to be accentuated and the aortic second sound is ringing.

The lungs are resonant, but at the posterior bases rales of chronic bronchitis or hypostatic congestion are heard. Now and then there may be a slight amount of fluid in the right pleural cavity. The liver is enlarged, as shown both by palpation and percussion. The urine is diminished in amount, of increased specific gravity, and may contain a variable percentage of albumin. If casts are present they are granular, or both granular and hyaline.

The course is henceforth either steadily from bad to worse, or, under treatment, tends for a time to general improvement. In the former event, œdema increases until general dropsy supervenes; the dyspnœa becomes orthopnœa, with possible paroxysms of veritable air hunger. The heart grows more and more incompetent, with possible irregularities

in force and rhythm. Hepatic stasis augments even to the point of epigastric pain and tenderness. The lungs grow distinctly œdematous, and the urine is scanty and highly albuminous. The clinical picture has now become that of extreme myocardial insufficiency from whatever cause. The end to the struggle comes slowly and gradually, or, after weary months, the worn-out heart stops suddenly.

Should treatment, on the contrary, improve the condition, the reinstatement of heart power is but partial and often transitory. In the case of a rich man, a journey to Bad-Nauheim is succeeded by such a gain in strength that he is able to return to his office the following winter. Or, the less fortunate workingman finds so much relief from rest in bed in a hospital ward, that when discharged he flatters himself he can resume his arduous vocation. In either case the man sooner or later again grows conscious of the approach of his old enemy. This time the symptoms, if they yield at all, do so with greater reluctance than before. Thus, with discouraging repetitions, the patient drags on until death terminates the unequal fight, either abruptly and unexpectedly, or in the midst of all the phenomena which mark extreme myocardial inadequacy. In not a few instances it is a secondary pneumonia which closes the scene.

Cases Associated with Chronic Nephritis.—In the class of cases just depicted the urine is not normal, but if the kidneys are diseased their condition is wholly subordinate to that of the heart. In those now to be described the primary disorder is a chronic nephritis, commonly of the interstitial variety, but many times of a mixed kind. There has been abnormally high tension for years, which, directly prior to the breakdown, may reach the enormous figures of 225 or even 260 mm. It is this excessive peripheral resistance which is responsible for the development of myocardial inadequency, and when at last serious symptoms set in they are in reality those of cardiac rather than renal incompetence, although the latter supervenes in time.

Usually the first symptom is shortness of breath on exertion. In some cases it is vertigo which appears while the man is walking in the street. As time goes on this breathlessness grows into outspoken dyspnœa. It is apt to be associated with unwonted nervousness and more or less decrease in strength. Some patients suffer to such a degree from dyspnœa, nervousness, and insomnia that their days and nights are a series of unendurable torture. In search for relief they tramp and work until exhausted, and then go to bed in hope of repose.

If the heart is examined at this time, it is found hypertrophied and beating with increased frequency in the attempt to overcome the resistance offered by the abnormal pulse tension. The sounds may be clear but the first at the apex is short and valvular and the second sound doubled so as to produce a gallop rhythm. The aortic second sound is loud and ringing, and in some cases is the most marked feature in the examination. Accentuation of the pulmonic second tone indicates the heightened blood pressure in the pulmonary vessels, but other signs of congestion within the lungs are not very manifest. The excessive pressure in the aortic system is overpowering the myocardium.

Appropriate treatment ameliorates the condition for a longer or shorter

period. Yet, if examined, the pulse is found habitually tense and too rapid. Hypertrophy still predominates, but is slowly yielding to dilatation. There are no pronounced cardiac symptoms, and yet he is aware, every now and then, of breathlessness or palpitation and of a want of his old-time vigor and endurance. At length, either in consequence of injudicious physical effort or because the degenerated myocardium has yielded to the dilating force of the persistently high-pulse tension, the patient's dyspnœa reasserts itself. From this point forward the symptoms are those of myocardial incompetence.

Examination of the heart now shows a combination of hypertrophy with dilatation which is apt to involve chiefly the left ventricle. The area of deep-seated dulness is not quadrangular as in the preceding group of cases, but extends to the left to a variable distance outside the nipple line. The apex beat is diffused and uncertain, and the palpating hand appreciates an indistinct doubling of the impulse. Upon auscultation, this diastolic tap is found to correspond to a reduplication of the second sound, which imparts to the tones a more or less characteristic gallop rhythm. There may or may not be also a systolic apex murmur depending upon the degree of dilatation.

The pulmonic second sound is intensified and the aortic is diminished, but more sharp and metallic. The pulse is of increased frequency, 110 to 125, and regular or now and then faltering or intermittent. The radial artery is hard to compress. The sphygmomanometer still records hypertension. The liver is apt to be palpable and may be tender. In many cases it is firmer and thinner than in pure congestion of the organ. As proved by the subsequent history, it is cirrhotic. The urine is less abundant than formerly and usually contains albumin and casts. The ankles may pit slightly, but in the beginning of this final struggle are not markedly œdematous. In some instances dropsy is wanting.

The course is now very like that in any other case of cardiac inadequacy, but the patient's dyspnœa, restlessness, nervousness, and increasing weakness are apt to be more pronounced than in the incompetence of valvular disease. Under the combined influence of powerful cathartics, a restricted dietary, and the inherent tendency of the albuminuria, the patient gets into a state of hydremia which results in general dropsy and, finally, ascites.

Not infrequently this state of malnutrition brings on acetonemia or a form of toxemia which is an *inanition toxemia*. The patient is not actually delirious but is drowsy and not clear in his mind, while at night he may actually show mental rambling and sometimes excitement. In some cases the toxemia is of an *hepatic* origin and closely simulates uremia. The breath is heavy and foul, and the sensorium is decidedly obscured. The breathing may assume a Cheyne-Stokes type.

The heart is now still more dilated; a tricuspid, regurgitant murmur has become added; the external jugulars pulsate visibly; the liver is still more engorged; the pulse is irregular, intermittent, or too arhythmic to be accurately counted. It is feeble and the sphygmomanometer now shows an abnormally low tension, 105 or even 90 mm. The state of things is truly pitiable and the fatal termination is only a question of time. Death

may come suddenly when the patient seems in the same condition as for many weeks, certainly a very merciful ending, or the feeble spark of life may simply flicker out; or uremic coma may terminate the struggle; or the exitus may take place in consequence of pulmonary œdema.

Some of these nephritic cases show wonderful tenacity of life so far as the heart is concerned. According to the writer's experience they are those which display predominating dilatation of the right heart. The left ventricle is also dilated and the mitral valve leaks, but the behavior of the organ as a whole points to degeneration and stretching of the walls of the auricles and right ventricle as the leading feature. The action of the heart is so arhythmic that one can aptly apply the term delirium cordis.

The excretory ability of the kidneys is greater than might be supposed from the degree of albuminuria, and they often respond well to such a remedy as diuretin. But the drain on the system tells surely though slowly, and the anasarca is largely hydremic, as shown by the softness of the tissues on pressure. Nevertheless, it is the myocarditis even more than the nephritis that is surely dragging the patient to his grave. Part of the clinical picture is owing to the albuminuria, it is true, but it is the incompetence of the heart muscle which is mainly responsible for the dyspnœa. That it is not stasis, solely, which causes the dropsy in all cases, is proved by its diminution or disappearance after chloride of sodium has been withdrawn from the dietary.

In not a few instances the œdema is so slightly influenced by a non-chloride diet that venous stasis must be regarded as a principal factor in its production. It is these cases that are so intractable to treatment, and which pursue a steadily downward course and terminate in months at the outside. There is a vicious circle of conditions which precludes all hope of recovery, but the fact that other than palliative measures are without avail from the moment the abnormally high gives way to low blood pressure, proves that the chronic myocarditis has become the reason for our defeat, if, indeed, it were not so from the outset.

Cases with Angina Pectoris.—A relatively small number of cases display, as their leading feature, more or less typical attacks of Heberden's angina. In strictly classical examples of this, the heart may display some degree of hypertrophy and the aortic second sound is clear and ringing, but more obvious departures from health are seldom present. The radial arteries may be sufficiently stiff to roll under the palpating finger, but the pulse may not show marked tension and be quite regular. This form is most often seen in elderly men, and the condition primarily responsible for the anginal seizures is sclerosis of the coronary arteries. The myocardium is secondarily affected, but is still competent so far as can be measured by symptoms.

There is another form in which evidence of cardiac incompetence is so plain as to warrant the diagnosis of chronic myocarditis. The attacks of pain may not be exactly typical, and yet are sufficiently so to render clear in what category they belong. The heart is found dilated and feeble; its action is too rapid and is irregular, although not always very arhythmic; the sounds are weakened, the aortic second being accented and

there being a systolic murmur in the aortic and, perhaps, also in the mitral area. Such a patient presents more or less shortness of breath, although this is quite apt to be ignored in consequence of the greater impression made by the angina. There may be a demonstrable engorgement of the liver, and impaired resonance with subcrepitant rales may be discovered at the base of the lungs behind. The urine may or may not show albumin and casts, but for the most part chronic nephritis is a minor consideration. The peripheral arteries are moderately sclerotic, and blood pressure is raised.

In the former type of cases the angina pectoris dominates the clinical picture up to the end, which is very apt to occur with more or less suddenness. The second class of cases may likewise terminate by sudden death, but in some instances the symptoms of myocardial inadequacy increase until they display the characters of the preceding groups.

Cases of the Senile Heart.—One not infrequently encounters old people of both sexes whose hearts, if examined by the pathologist, would display the changes of myocardial degeneration, yet who enjoy a state of health that is truly surprising. The pulse is more or less irregular and sometimes so arhythmic as to startle the physician. Its tension is increased to 145 or 165 mm. Hg., and the arterial coats feel stiff or even beady. The apex beat is displaced outward and downward in consequence of combined hypertrophy and dilatation. The sounds are accompanied by systolic murmurs both at the apex and in the aortic area, while the second tone is ringing and possibly impure. The urine shows changes that go with this cardiovascular degeneration, namely, nocturnal increase, low specific gravity, a trace of albumin at times, and granular and sometimes hyaline casts. Stasis in the portal vessels is not marked, but digestive disorder shows itself by flatulent distension of the bowels and eructations.

The majority of such old persons keep tolerably well so long as they follow the even tenor of their way. So soon, however, as they overdo in some manner, and, particularly if they contract a bronchitis or some other ailment, they show at once how little resisting power they possess. The heart at once evinces its intrinsic feebleness, which it is important to recognize early and endeavor to arrest before it grows more serious. These patients are very likely to succumb to pneumonia or influenza. In many of the cases the chronic myocarditis is but an incident in old age, and, so long as the heart is potentially equal to its ordinary work, it requires nothing more than protection against additional demands. In other cases distinctively cardiac symptoms may make their appearance and pursue the usual downward course. In not a few instances these old hearts rally in a wonderful manner, under skilful management, and then may be bolstered along for months and even several years.

Cheyne-Stokes respiration may appear and persist in a more or less typical form. In other instances it may disappear after a time or show itself only when the patient is asleep. It does not depend upon the state of the myocardium so much as upon the condition of the vessels in the medulla, and hence the blood supply to the respiratory centres.

Precordial pain may or may not be experienced, but in the cases

considered typical illustrations of the senile heart it has been the exception. In a few instances angina pectoris has been a leading feature and in others there has been a dull pain in the cardiac region, which, however, was subordinate to other symptoms.

The *pulse* presents all possible variations in rate and rhythm. It is more apt to be too frequent than too slow, and there may be paroxysms of tachycardia of uncertain duration. When these subside they leave the patient much exhausted. They may be an expression of cardiac asthenia and after several months of treatment the pulse, previously very weak and arhythmic, becomes regular and fairly strong. Irregularity of the heart's action is a marked feature of many cases. In other cases irregularity shows itself only during some physical effort and then evinces the potential feebleness of the myocardium.

Cases Presenting the Stokes-Adams Syndrome.—Abnormal slowness of the pulse, to which earlier writers used to attach so much importance in the diagnosis of fatty degeneration of the heart, is far less common in chronic myocarditis than is increased frequency. The cases in which the writer has observed habitual bradycardia were in middle-aged men with general enlargement of the heart. Now and then a case is encountered in which the myocardial incompetence is attended with paroxysms of recurrent bradycardia of such striking character as to merit a separate clinical grouping.

These cases are marked by recurrent spells, which, originally described by Stokes and Adams, have been named after these eminent Irish observers. These attacks are characterized by recurrences of such extreme slowness of the heart's action that the brain is inadequately supplied with blood, and hence the individuals suffer also from vertigo or even syncope. In some instances the seizures so closely simulate an epileptic fit, that they have been mistaken for convulsions of this nature. Although not confined to persons of middle or advanced age, still these attacks of recurrent bradycardia are most often seen in individuals whose various organic lesions, if not their actual age, place them in the category of senility. These patients usually, but not always, die suddenly, probably from heart-block during one of their attacks.

Cases of Rupture of the Heart.—Chronic myocarditis occasionally terminates abruptly through rupture. The mishap is announced by symptoms denoting grave cardiac failure: precordial pain or oppression, rapid, feeble pulse, cold extremities, and pale, anxious countenance; in short, the symptoms of collapse. The area of heart dulness is increased, and the tones are distant and weak. Death supervenes after a shorter or longer period, from a few minutes to many hours, and a correct diagnosis is usually made only at autopsy.

Cases of Aneurism of the Heart.—Symptoms by which this condition may be recognized are rarely occasioned. Such as exist are attributable to myocardial inadequacy. If the aneurism be very large it may so modify the outline of cardiac dulness as to lead to a correct diagnosis. In very rare cases there may be bulging of the chest wall in the vicinity of the apex, and this tumor may pulsate so as to simulate a double apex beat. The symptoms are in effect those of cardiac dilatation.

Cases Simulating Valvular Disease.—It is not very uncommon to encounter individuals of forty or over who manifest symptoms of cardiac insufficiency, and who, on examination, are found to have signs of mitral or aortic valve disease. Sometimes it is a mitral regurgitation, sometimes an aortic leak, and occasionally there is evidence of slight stenosis associated with the incompetence of the mitral valve. There is no clear history of rheumatism, but there is often a statement of some antecedent strain. These cases present nothing peculiar in their symptomatology, but should be carefully studied to ascertain the state of the heart muscle. Pulmonary œdema occasionally occurs in these patients.

The prognosis and, to a certain extent, the nature of the treatment depend upon the degree of damage sustained by the myocardium. This may permit dilatation during life and consequent reflux through the mitral orifice. Instances of aortic insufficiency, of the kind now considered, are probably always secondary to syphilitic mesaortitis and not endocarditis. They may be quite appropriately regarded as cases of cardiac lues, yet their development is so insidious that recognition of the leak generally takes place after its complete establishment, and compensating hypertrophy has occurred. In several such instances the myocardium has been found extensively degenerated.

Symptoms in these cases of pseudovalvular lesions are of the kind seen in failing hearts from whatever cause, but there are generally clinical data pointing to degenerative changes in the arteries, kidneys, and liver which assist in the *intra vitam* recognition of vascular and myocardial decay as the fundamental condition. Such cases are extremely common among negroes, in whom they probably have a syphilitic origin.

Symptoms of the Fatty Heart.—There are undoubtedly cases of fatty overgrowth and infiltration which deserve the term *fatty heart* or *cor adiposum,* but it is an error to suppose that all obese individuals have this kind of heart. It is likewise erroneous to infer that corpulent persons exhibiting signs of myocardial incompetence necessarily have fatty hearts. Furthermore, a heart that is enveloped in a thick layer of adipose tissue may be capable of performing its functions without evincing special weakness. These considerations render the term fatty heart objectionable, from a clinical standpoint. It would be far more in accordance with facts to adopt the term, *myocardial incompetence of the obese.*

The symptoms in this class are not peculiar, but are essentially those of cardiac inadequacy from other causes. When they arise it is usually in consequence of the heart's inability to longer endure the heavy strain imposed upon it by the obesity. Not only is the work of the organ magnified by reason of the individual's weight, but the new vascular areas which have been developed put additional burden on the central organ of circulation. The heart is required to do an extra amount of work that is commensurate with the degree of obesity. Some corpulent individuals, moreover, are anemic and the myocardium is inadequately nourished. This is one reason why some fat persons develop symptoms of cardiac incompetence at a comparatively early age.

The fat and anemic are in danger of overtaxing their hearts by unusual

exertion, but, warned by their shortness of breath, rarely commit acts which seriously overstrain their heart walls. The fat and muscular, on the other hand, often subject their hearts to enormous strain and consequently form the class in which myocardial insufficiency is the more frequently seen. If the arteries are stiff, or if blood pressure has been high for many years in consequence of excessive intra-abdominal blood pressure, chronic nephritis, etc., the myocardium may be in a state of degeneration and hypertrophy. In such a case the condition is in reality a chronic myocarditis, not a fatty heart.

In a minority of cases the heart is neither fatty nor degenerated; it is simply inadequate because of the disproportion between its potential strength and the burden it has to carry. The organ has hypertrophied to its limit and then, being unable to hypertrophy further, it dilates. This is the first step and now distinctive symptoms appear.

Breathlessness on exertion is so usual in corpulent individuals that it is lightly regarded by them. Now, however, myocardial incompetence causes them to puff and blow in a way quite unusual, and upon relatively slight exertion. Dyspnœa is now fully established and in some instances may be fairly constant. From this time on to the end it remains a marked feature.

The pulse is increased in frequency and regular or irregular as the case may determine. Its tension is usually augmented in the beginning, but tends to fall with progress of the inadequacy. In cases in which chronic myocarditis, secondary to renal disease or excessive intra-abdominal blood pressure, does not coexist, the tension of the pulse may not be noticeably raised even with subjective symptoms.

Examination of the precordium is generally unsatisfactory. The cardiac impulse is not perceptible on account of the *panniculus adiposus*, and for the same reason it is difficult to obtain definite data by percussion. Auscultatory percussion may enable one to obtain a fairly reliable outline of the area of dulness. Upon auscultation the sounds are distant and feeble, and murmurs are generally wanting. Careful attention may detect special feebleness of the first tone at the apex, and accentuation of either the pulmonic or aortic second sound. It is possible that after the patient has been required to hop about the room, or to ascend a flight of stairs, a soft blowing murmur may develop in the mitral area. This sign, which is so commonly elicited in cases of myocardial insufficiency, is an exceedingly important finding, since it indicates dilatation of the ventricle occasioned by exertion.

As a rule, fat people rarely exhibit as marked evidence of turgescence of the superficial vessels as do thin individuals. Indeed, capillary stasis may only give them a ruddy or plethoric appearance which may be mistaken for the hue of health. It may quite disguise the degree of anemia actually present. The abdominal corpulence also prevents palpation of the liver, and hence stasis in this organ may not be detected. Puffiness of the ankles may be present in the beginning, and as circulatory activity decreases may at length merge into actual œdema. The urine may present the changes of renal stasis or nephritis. In brief, the clinical picture is that of more or less extreme heart failure. The background

of the picture is ever the same; it is only the details and coloring which are different, and these are determined largely by the degree of obesity.

Diagnosis.—Acute Myocarditis.—Not only is this a matter of difficulty and often of uncertainty, but the physician must endeavor to decide which form is present. He should never lose sight of the possibility of acute myocarditis in the course of infectious diseases, especially influenza and diphtheria. Instability of the pulse, marked pallor and vomiting, restlessness or listlessness and apathy, are symptoms which should arouse suspicion of acute myocarditis. If, in addition, the heart becomes dilated and the tones feeble, there is good reason for assuming parenchymatous degeneration of the myocardium. A soft, systolic murmur often develops which, confined to the vicinity of the apex and accompanying but not replacing the first sound, is thought to indicate endocarditis. Such a bruit may, however, in many cases be caused by relaxation of the ventricular muscle, in consequence of which the mitral valve is not accurately closed. It is, therefore, the murmur of muscular mitral insufficiency, and in suspected cases affords corroborative testimony of the existence of some degree of myocarditis.

Interstitial, *i. e.*, suppurative myocarditis, may be suspected in the course of pyemia or puerperal sepsis if the clinical picture resembles that of malignant endocarditis with embolic phenomena, yet without distinct signs of valvulitis. In this as well as in the parenchymatous form, however, the diagnosis will generally be by inference and can rarely be absolute. In any case the probabilities are in favor of the parenchymatous rather than the interstitial variety.

Chronic Myocarditis.—The diagnosis of this affection may or may not be difficult in accordance with the extent and character of the changes in the heart and arteries, and the data furnished by the patient's history and symptoms. Cases may be divided into two main groups, as follows: (1) those in which the symptoms and clinical findings leave no reasonable doubt of their real nature, and (2) those which present equivocal evidence of arterial and cardiac disease, yet are at a time of life that renders probable the existence of degenerative changes. The former group interests the physician as a clinician and therapeutist, while the latter concerns him as a diagnostician and life-insurance examiner.

1. In this division of cases age is important, since if symptoms of heart disease develop in a person who has passed the prime of life, it is a fair assumption until proved otherwise that decay of the heart muscle is responsible. This is greatly strengthened by the failure to discover, in the history or physical signs, evidence of a lesion caused by endocarditis or pericarditis. If in addition the accessible arteries are sclerotic and the urine shows the changes of chronic nephritis, or if in the absence of demonstrable changes in the vessels or kidneys, the pulse tension is abnormally and persistently high, there is good ground for believing that the myocardium has experienced a serious degree of degeneration. If the area of dulness is found increased transversely; if the first sound at the apex is valvular and feeble or impure, perhaps accompanied by a circumscribed soft murmur, and if the aortic second tone is clanging,

especially if in addition there is dilatation of the aorta, then the diagnosis of chronic myocarditis may confidently be made.

On the other hand, it must be borne in mind that serious myocardial incompetence may exist with but few physical signs. The area of deep cardiac dulness may be but slightly increased and the tones may be free from bruits, presenting no other change than enfeeblement of the first and accentuation of the second sound in the mitral or aortic areas or both. Nevertheless such inconspicuous modifications taken in connection with age and subjective symptoms may furnish just the evidence required. Should the physician still be in doubt, the effect of brisk exercise on blood pressure and pulse rate is likely to settle the question. As shown by Gräupner, a healthy heart responds to brisk exercise not alone by acceleration of the pulse, but also by increase of systolic blood pressure which remains raised over its original figures after the pulse has returned to its former rate. The pressure may then continue to rise or after a decline may again show an increase known as the secondary rise. In cases of incompetent myocardium the blood pressure according to the degree of inadequacy may first rise but slightly and then fall rapidly to or below its original level, and before the pulse regains its former rate, or it may fail of any increase at all, but instead show a decline. Accordingly if a middle-aged person gives this blood pressure evidence of myocardial incompetence, together with some of the data obtained by physical examination, it is a fair assumption that degeneration is responsible.

As a matter of fact the recognition of myocardial inadequacy is rarely difficult. The real problem to be solved is the underlying state of the heart muscle. Therefore when cardiac symptoms occur in a person under forty-five without valvular disease the real pathology of the case must be determined by close attention to the previous history as well as accurate investigation of the physical findings. The history of syphilis, of the abuse of alcohol, of gout, chronic plumbism or of severe infections strengthens greatly the probability of myocardial degeneration. If in addition the blood pressure is persistently too high or too low, or if the urinary findings indicate beginning renal change, or if anginoid pains are complained of, the case had better be regarded as serious rather than dismissed with the assurance that nothing is the matter.

2. Diagnosis in this class of cases is often very difficult. Subjective symptoms of myocardial insufficiency are wanting or are so inconspicuous as to escape notice. Moreover, the individual may present the appearance of perfect health and may not have reached an age that in itself suggests the possibility of degenerative change. As stated already, it is just this type of person that comes up for life insurance and taxes the skill and judgment of the examiner to the utmost. As a fundamental step there should be a minute and rigid inquiry into the history, and attention must be paid to such illnesses and habits as may be of etiological importance.

Undue frequency of the pulse at the time of examination may result from apprehension or nervousness and not indicate heart weakness. Its real significance should be determined through repeated examinations or by studying the effect of posture. In the dorsal decubitus the pulse rate should fall from seven to fifteen beats from that in the standing

position, while when myocardial incompetence is present the rate in the recumbent posture may not fall. Should this test prove inconclusive, then the effect of brisk exercise on blood pressure should be ascertained. Auscultation of the heart immediately succeeding hopping often assists in diagnosis, since if the myocardium is not equal to the effort it may be evinced by a soft systolic murmur at the apex indicative of slight dilatation and muscular mitral insufficiency.

Examination of the heart before exercise in these latent cases, as they may be termed, may or may not yield definite information. In some instances deep-seated cardiac dulness is plainly increased and the tones present some easily recognizable deviation from normal, such as feebleness of the first and undue intensification of the second sound, especially in the aortic area, where it may be quite metallic or clanging. Or there may be a systolic bruit of greater or less distinctness in the second right interspace which together with accentuation of the second tone suggests sclerosis of the aorta. Should the physician not be able to ascertain the size and shape of the heart by percussion, he should have recourse to a skiagraph. Yet in many cases the estimation of the blood pressure will assist materially in determining the area of cardiac dulness, since an abnormally and persistently high pressure renders probable the existence of hypertrophy, and hypertrophy of the heart in a person of middle age may be regarded as synonymous with degeneration even though the potential integrity of the myocardium may not yet have suffered appreciably. Finally, other corroborative testimony may be found in the state of the accessible arteries, in slight but significant changes in the urine, and in evidences of visceral congestion.

Before closing this portion of diagnosis, it is well to say a few words concerning the recognition of myocardial incompetence in *women*. In them percussion of the heart is often impossible because of the mammary development, and yet there may be certain symptoms which make myocarditis highly probable. Under these circumstances valuable information may be obtained by careful palpation of the heart's impulse. It will often be perceived that the impulse is diffused and extends too far to the left. Upon auscultation the first sound at the apex is not clear and strong, but valvular, or actually impure, and the aortic second is accented. In other instances it is the pulmonic second that is intensified. If in addition the pulse tension is too high, and the woman suffers from greater breathlessness on exertion than should be the case in relation to weight or anemia, and if she be leading a strenuous social, domestic, or club life, the assumption is tolerably safe of a chronic myocardial weakness, and if the age be fifty or thereabout this weakness probably rests upon a basis of chronic myocarditis.

The Fatty Heart.—The existence of fatty overgrowth and infiltration to an extent occasioning myocardial incapacity must be a matter of inference rather than clinical demonstration. In the majority of fat persons who present cardiac symptoms the most we can do is to diagnose the incompetence. If the individual is very fat and at the same time anemic, is too young to warrant the assumption of cardiovascular and renal degeneration, and accordingly fails to furnish clinical proof of such

degenerative changes, we may recognize heart strain as probable without degeneration. The case may then be said to come within the category of the myocardial incompetence of the obese. As a matter of practical interest it is not necessary to know whether the heart is actually fatty or not; it is overpowered by the general obesity, and this of itself forms a sufficiently serious condition.

Prognosis.—This is necessarily grave, since whatever impairs the structural integrity of the heart muscle is likely to limit its potential capacity. The heart is, however, a marvellous organ, whose possibilities for compensatory adjustment to altered conditions enables it to perform its function in a way that is truly astonishing. Accordingly it may be performing its work with but slight evidence of anything being wrong, while all the time a process of degeneration is going on.

Acute parenchymatous myocarditis may be recovered from, when not extensive, but the possibility of sudden death should always be borne in mind, especially during the course of diphtheria and even after convalescence. On this account a child should be kept under close observation, both when at play and at rest, for the detection of slight signs of incompetence. The *interstitial form* of acute myocarditis is probably always fatal, unless it be very circumscribed, which is not usual.

Chronic myocarditis also carries with it the liability to sudden and unexpected death, and since we possess no means of determining the seat of dangerous lesions, we must always regard as uncertain the life prospect in any individual with myocardial degeneration. Nevertheless, if hypertrophy predominates and symptoms of inadequacy cannot be discovered, we may hope that the potential integrity is still such as will preserve the heart from incompetence so long as it is not too greatly overtaxed. When signs of incompetence once appear, prognosis becomes very serious and must be reckoned by the degree of insufficiency manifested, or by the response shown to proper treatment.

Persistent arhythmia is generally held to be of worse import than is regularity even with tachycardia when this latter is not extreme, and yet one should look with apprehension on an habitually accelerated and regular pulse. Although irregular hearts may endure for years without distressing symptoms, still they always carry with them the possibility of sudden disaster. Degeneration of the left ventricle is more serious than degeneration of the auricles, and it is in the latter condition that arhythmia is so common; while, according to Hampeln, extensive fatty change in the wall of the ventricle is compatible with perfect regularity of action. When polygraphic tracings show a persistent arhythmia to be due to auricular fibrillation or interference with stimulus conduction to the ventricle, or when digitalis skillfully administered fails to correct the irregularity, the prognosis may be considered as grave.

Angina pectoris is of evil prognosis, since, in the majority of cases, there is more or less interference with coronary circulation, and this condition always carries with it the possibility of sudden death. The prognosis in cases of myocardial incompetence, associated with chronic nephritis, is likewise very bad. The heart muscle may be assisted in

doing its work for a time after the initial manifestations of its weakness, but when the break again occurs the mischief is likely to be irreparable. The development of gallop rhythm always, in the writer's experience, has portended a not very remote termination in death. This rhythm may persist for months, but it indicates a degree of strain of the ventricular wall to which it must inevitably yield in time. A heart weakened by chronic myocarditis may be capable of performing its functions, fairly well, so long as some extra burden is not imposed. Any illness may prove the last straw. This is particularly true of acute infections.

Fatty heart, or the cardiac incompetence of the obese, is extremely serious and is rarely recovered from when it has become pronounced. The more corpulent the individual the worse the prognosis, since it is hardly likely that the obesity can be materially reduced without endangering the nutrition of the heart muscle.

Treatment.—Preventive.—There is an aspect of prophylaxis which even, as regards acute parenchymatous degeneration, falls within the limits of professional possibility. This is the prevention of heart strain, which is oftentimes the factor that induces myocardial incompetence. Efforts in this direction must be both educational and therapeutic. "What," the writer was once asked, "are we to do to preserve the heart of the elderly man whom we find has signs of myocardial weakness?" The reply first suggesting itself is: Inform him of his danger if he subjects his heart to avoidable strain. He should be told not to run for trains, not to climb mountains, not to commit excesses in baccho et venere, not to overeat, not to smoke strong Havana cigars to excess—in a word, not to do those many things which are likely either to dilate the heart acutely or to tax habitually its limited powers of endurance.

If a man is leading a too stenuous business life, he must be warned of the positive danger lurking in its continuance. If a woman is devoting herself too strenuously to social functions, charitable or club work, etc., she must be told to limit them and take life more easily henceforth. If the physician will take the trouble to inquire minutely into the history of a patient, for weeks or months immediately prior to the initiation of his symptoms, he will be surprised to learn how often there has been some unusual strain as the real determining cause of the myocardial breakdown. Therefore, the physician must make good advice paramount to prescriptions, in the case of persons whose hearts are no longer sound.

High blood pressure must be lowered if possible, or at least kept from becoming still higher by restriction of the dietary, by cathartics, and, in women, by regulation of the clothing when this is too tight. Not only is the food to be restricted to an amount the caloric value of which is not excessive, but articles rich in purin bases must be cut out as well as those which lead to intestinal fermentation. Flesh foods in particular must be taken moderately, and strong stock soups and broths must be forbidden on account of their extractives, which stimulate heart action unnecessarily. Fried dishes are injurious because of the fatty acids they contain, and must be interdicted.

The daily drinking of immoderate quantities of water increases the labor of the heart, and should be stopped. Strong coffee and tea abound

in purin bases and also tend to endanger the integrity of the myocardium by exciting the heart, and whatever puts unnecessary work upon it tends to its ultimate enfeeblement. For this reason alcohol is bad for these patients and should be forbidden. The smoking of strong Havana cigars often accelerates the heart and is said to augment blood pressure. They must be forbidden, reduced, or replaced by mild cigars.

The occasional use of a mercurial and saline *cathartic* is very beneficial in this class of cases. Many of these persons declare they do not require such remedies, because they are and always have been perfectly regular in the matter of a daily stool. The cathartic is not ordered because of constipation, but because most of the patients who have high-pulse tension show abdominal corpulence, or a marked tendency thereto, and, being hearty feeders, generate injurious toxins in their intestinal tract. For such individuals it is highly beneficial to order a thorough removal of these toxins by a brisk cathartic. This is particularly advisable the morning after a banquet or dinner party. It is often truly remarkable how much better these people with high tension breathe and appear, after such a cleaning out of their colon. In some instances the blood pressure falls appreciably after a calomel and saline purge.

Tight clothing about the abdomen is a serious menace to women with high tension, since whatever occasions pressure upon the abdomen tends to raise blood pressure through the action on the splanchnics. It is on this account that deep massage of the abdomen is especially harmful to patients with chronic myocarditis. Medical gymnastics are of the very greatest utility in the preservative management, especially for persons who are obese or have an excess of abdominal fat.

The most beneficial exercises are not the so-called resistance exercises, but breathing exercises and other light gymnastics, all performed with the assistance of some person who is trained to this work and can be trusted not to carry the various movements to the point of causing embarrassment to the respiration and circulation. More than one man, who was beginning to evince symptoms that threatened before long to merge into pronounced myocardial incompetence, by means of such exercises, carried out for a number of weeks, has been restored to a condition of such comfort that he considered himself entirely well.

Self-resisting exercises, which may be excellent for persons with sound hearts, are attended with the possibility of harm; so also is the use of certain mechanical devices for exercise, since in his enthusiasm the individual with high-pulse tension, or an already hypertrophied heart, is likely to put himself seriously out of breath and embarrass his heart.

The purpose of these exercises is to ease the work of the heart, and whenever they cause palpitation or actual dyspnœa, the myocardium is being overtaxed, not lightened of its labors. Golf is an excellent form of exercise for this class of patients, provided it is not played too violently or for too long a time. Walking is also beneficial, but, like golf, must not be continued to the production of much weariness and must not be at a pace that induces shortness of breath and palpitation. Oertel's hill-climbing or "terrain kur" is likewise good when carefully supervised by a physician. In fact, almost any form of muscular exercise may be

made beneficial which promotes easier breathing and a more active circulation without great fatigue. *Per contra,* whatever produces dyspnœa, palpitation, or a sense of fulness and discomfort in the precordium is fraught with danger to persons who show breathlessness or portentous elevation of blood pressure.

Medicinal agents play a minor rôle in the prevention of myocardial incompetence. When arterial hypertension is dangerously high, it may be necessary to prescribe remedies which exert a vasodilator action, in the hope of lessening vascular resistance, but unless judiciously administered they may result in harm instead of benefit. Nitroglycerin, sodium nitrite, erythrol tetranitrate are the drugs most commonly employed. The action of nitroglycerin is rapid and too evanescent to be of much real service. Nitrite of sodium is less transient in its action and may be given in doses of 1½ to 2 grains without producing the headache so commonly experienced after nitroglycerin. Erythrol tetranitrate is said to exert a still more sustained effect than the remedy just mentioned. It may be given in doses of ½ grain every three or four hours. Even as regards these two remedies, candor compels one to express the same skepticism concerning their ability to reduce pulse tension materially unless their action is reinforced by other measures.

Palpitation is quite commonly experienced by persons with hypertension, especially upon some physical effort not great in itself. This symptom, as well as the slight breathlessness that may accompany it, probably is an initial sign of dangerous heart strain. It may be lessened by the careful administration of sodium nitrite together with tincture of aconite in those cases in which digitalis appears to aggravate the annoying symptom, but as aconite is capable of producing harm, it is better to attempt the control of the palpitation by restricted diet, cathartics and rest in bed before resorting to remedies.

Management in the Stage of Incompetence.—The character of the changes in the heart and their association with degenerative lesions in the bloodvessels and kidneys preclude all thought of restoring the heart to a condition of health. The most that can be hoped for is an improvement in its working capacity. Some patients respond to treatment in a truly remarkable manner, while others appear to possess no recuperative power at all. In the former class all that seems necessary is to ease up the work of the organ by rest, to reduce congestions by cathartics, and to give the heart a lift, as it were, by some cardiac tonic, and the machinery goes on again nearly the same as before.

In the second class it soon becomes apparent that the mechanism is bound to run down in spite of all efforts. Unfortunately these form the majority, and consequently the treatment of myocardial incompetence may be pronounced most unsatisfactory. This is emphatically true of the nephritis cases. In them the hypertension is so great as to prove an insurmountable barrier to restoration of heart power. Whatever improvement may be gained in the beginning is soon lost and rarely if ever returns. Before long the hypertension is succeeded by hypotension, and with this the doom of the patient is sealed.

Rest.—We possess no measures for the treatment of myocardial insufficiency which are different from those applicable to the broken compensation of valvular disease. There are certain conditions, however, depending upon the degenerative changes in the heart and other organs which compel us to modify somewhat the application of these measures. Foremost among the limited means at our command is the enforcement of physical rest. It goes without saying that if the heart is unequal to the demands made upon it, these demands must be lessened. Accordingly, if an individual suffers from dyspnœa on effort, he must not make the effort but must rest his body in order to give his weakened heart a rest. The rigor with which this injunction is enforced must be determined by the degree of incompetence. In some cases this must be absolute in bed, while in others it may be necessary only to confine the patient to his room or to his bed, with permission to walk to the toilet when near by and on the same floor. In early cases, showing only or chiefly breathlessness on exertion, this amount of rest, with other measures, may be sufficient to restore the individual for a time.

If the left ventricle is greatly dilated and feeble, a condition which, under the strain of physical exertion, predisposes to sudden diastolic arrest, rest in bed should be absolute. In some of these cases paroxysms of dyspnœa (smothering spells) are so distressing that patients declare they cannot remain in bed. For such, it is often well to allay the subjective sense of dyspnœa and to produce quiet of mind as well as of body by the hypodermic administration of morphine.

Although absolute rest is essential *at first*, still it is not well to continue it for too long a time, especially if the heart has profited appreciably by the measure. The heart is the central organ of circulation on which the main work depends, but nature never intended this organ to carry on the flow of blood unaided. Various auxiliary factors are to be found in the elasticity of the vascular coats, in muscular contractions, and in respiratory movements. If now an individual with stiff arteries is compelled to lie perfectly still in bed for days together the factors of muscular action and respiration are largely abolished and the work of maintaining the blood flow falls more heavily on the left ventricle.

Because of the considerations just mentioned, it has long been the writer's practice, in cases of serious myocardial inadequacy, to supplement enforced rest from active, voluntary movement by passive exercises and massage, as will be again considered. It always seems well for these patients, who are allowed to break their rest by going to the toilet, sitting up, etc., to understand the strain put upon the weakened heart muscle by sudden assumption of the erect posture. Therefore, it is well to explain to them the injurious effect of rising quickly from the recumbent posture to the feet, since a damaged heart cannot always adjust itself promptly to the sudden muscular contraction thereby occasioned. The sudden increase of intraventricular blood pressure thus produced subjects the left ventricle to instantaneous strain. It is inability to withstand the dilating force of such an action which causes so many of these patients to die directly after having arisen to their feet. Accordingly, they should be told to make such changes slowly and cautiously.

Resistance Exercises.—In all cases of myocardial incompetence the heart should be assisted by properly conducted exercises, *i. e.*, resistance exercises. These consist of certain movements on the part of the patient made against resistance offered by a skilled operator; they must be executed with such gentleness and precision as not to impose any additional burden upon the weakened myocardium. If the degree of resistance is properly applied to the patient's condition, the movements lighten the labor of the heart.

When the myocardium is very feeble it is well to have the exercises made while the patient remains lying in bed. As his heart improves he may sit up during his resisted movements, while only after considerable gain in the strength of the heart has been made are the daily treatments to be taken in the standing position. In the same cautious manner are the exercises to be increased in number and duration. The precise mode of action of these resisted movements is not perhaps fully understood. They serve to divert the blood from the heart to the extremities and thus to reduce its dilatation. Whether they can do all that is claimed for them by some, they certainly are serviceable to this class of patients by affording them a beneficial rather than harmful mode of offsetting possibly injurious effects of rigid rest in bed.

Massage.—This is another excellent means of counteracting the harmful results of prolonged recumbency by promoting the return flow of the blood. The caution should always be imposed of not having the abdomen massaged deeply and strongly, since this raises blood pressure.

Nauheim Baths.—The ever-increasing stream of patients to Bad-Nauheim, Germany, attests the popularity and efficacy of the baths there given for the treatment of heart disease. In no class of cases is this form of hydrotherapy more beneficial than in those of chronic myocardial incompetence. As with other therapeutic agents this should not be left for a last resort, but should be instituted early, before marked dilatation has set in. The degree of improvement is often truly surprising.

There are a number of reasons that may make it necessary for the physician to treat his patient at home instead of sending him to Germany. Among them is the fact that the health resort in question is only open from the first of May to the early part of October. Accordingly, it is recommended that when the baths cannot be had at Bad-Nauheim, they should be given in the home or elsewhere by means of artificially prepared waters. Caution may be urged against the employment of such baths without careful study of their indications and mode of action, so far as this is understood. The manufacturers of the so-called effervescing bath tablets send out circulars which make it appear that this form of therapy is very easy and simple in its application, and that from the start the baths should be charged with carbonic acid. They say common salt or sea salt may be added to the bath, but is not essential. Now such statements are likely to do harm, since it is not customary at Bad-Nauheim to begin a course of treatments with carbonated waters.

Very feeble, dilated hearts do not require and will not endure stimulating baths, but need soothing, slightly tonic baths. Therefore, it is always well to begin with warm, saline, but not effervescing waters, and to

come to the use of carbonated baths very gradually and only when the temperature of the water is such as to make it stimulating, and when the heart has gained sufficient strength to enable it to respond to such energetic stimulation as results from cool, strongly saline and effervescing waters. Hence it is plain that unless care and judgment are exercised, this form of therapy may become injurious instead of beneficial.

Digitalis.—So great is the dependence upon this remedy in cardiac disease, that most practitioners prescribe it at once, so soon as they recognize signs of myocardial insufficiency. In the class of cases now considered, the selection of a heart tonic should be largely determined by the degree of arterial tension and the state of the vascular coats. If the blood pressure is high or the vessels are stiff, digitalis must be administered with judgment. If this caution is not observed it will frequently be found that dyspnœa and palpitation are augmented rather than decreased. This is particularly the case in the myocardial inadequacy following upon chronic nephritis. *Strophanthus* may be preferable in cases showing hypertension, and yet even this remedy is not always well tolerated or efficient. Whenever, therefore, these drugs do not relieve symptoms they should not be persevered with in increasing dosage, but be replaced by others or associated with a vasodilator.

Tincture of Aconite.—Experience has convinced the writer of its great utility in some cases. These appear to be such as manifest annoying palpitation and irregularity of heart action, especially under the use of digitalis. Doses of 5 to 10 minims (0.3 to 0.6 cc.) of the tincture of aconite root (U. S. P. 8) may be taken three or four times daily with very great benefit in many cases. The remedy does not appear to relieve dyspnœa so much as excited heart action.

Vasodilators.—These are sometimes highly serviceable in cases of dangerous hypertension. But little effect can be demonstrated from these agents upon pulse tension, and yet in conjunction with digitalis, strophanthus, and especially aconite they may afford marked relief. A combination which frequently gives decided benefit to the dyspnœa, as well as palpitation, is nitrite of soda and tincture of strophanthus. The exact dose of each remedy cannot be laid down, but must vary in accordance with the degree of tension and the signs of myocardial incompetence exhibited in each case.

Sparteine Sulphate.—This remedy, much vaunted by the French, is of service when there is marked arhythmia and the auricles are dilated. It will fail strikingly in some instances and prove highly efficient in others. Why this is cannot be satisfactorily explained. The remedy may be ordered in doses from $\frac{1}{8}$ to 1 grain (0.008 to 0.06 gm.).

Ammonia.—There are patients who do not bear drugs that slow the pulse and contract the vessels. Some of these show a tendency to bradycardia, while others do not, but manifest feebleness of the left ventricle. It would seem as if the heart needs stimulation and quickening in these cases rather than slowing, as if it were not able to handle the increased amount of blood entering it during its prolonged diastoles. At all events the aromatic spirit of ammonia, in 15- to 30-minim (1 to 2 cc.) doses every two hours, has produced a striking improvement.

Caffeine and Strychnine.—These are excellent remedies with which to sustain flagging hearts, when digitalis and strophanthus are not admissible. They are both given best by hypodermic injections, the former in doses of $\frac{1}{2}$ to 1 grain (0.03 to 0.06 gm.) several times a day, and strychnine in doses of $\frac{1}{60}$ grain (0.001 gm.) at three- or four-hour intervals. Large doses of strychnine are to be avoided.

Diuretics.—Remedies of this class are indicated in cases with œdema. Retention of sodium chloride in the tissues is in most instances a chief factor in the production of dropsy and hence dechloridization of the diet is essential to the reduction of this distressing symptom. But in addition it is often necessary to stimulate the kidneys by drugs. Infusion of digitalis is of course the ideal remedy to this end, since myocardial weakness and stasis are also present. Nevertheless recourse must be had sometimes to other drugs; of these diuretin has long enjoyed a great reputation. Administered in solution and in doses of 60 to 120 grains (4 to 8 gm.) in twenty-four hours it will in many cases greatly augment the flow of urine.

Theocin or theocin-sodium acetate is allied to diuretin in action and in some instances seems to stimulate diuresis when other remedies fail. It is administered in tablets of which three to four may be given daily, and in connection with an absolute milk diet over a period of several days has given the writer good results. Potassium salts and the well-known vegetable diuretics have rarely proved of much avail in the writer's experience, but of the latter apocynum cannabinum is probably the most likely to prove efficacious.

Cathartics.—These may be mentioned in connection with diuretics, since they also prove a powerful means of removing œdema. To this end they should be as unirritating as possible, and must be given in such amounts as will produce many copious watery stools every day or every other day. One great reason why physicians fail to secure the effect desired over the dropsy and the hepatic stasis lies in their failure to recognize the clinical fact that, since transudation of serum is constant, its removal by means of hydragogue cathartics should be accomplished daily and not occasionally. Sulphate of magnesia in saturated solution and elaterine are the most efficient remedies of this class. The former is disagreeable to taste but is not drastic; $\frac{1}{2}$ ounce in 1 ounce of water may be taken hourly until the desired result is obtained. Elaterine is apt to excite emesis, but will certainly cause the evacuation of large amounts of fluid when calomel and other cathartic remedies fail.

Of course the repeated and prolonged use of remedies calculated to remove dropsy will in time be followed by emaciation and anemia, in consequence, partly, of the daily loss of important salts contained in the serous transudate and the copious, fluid stools. Deplorable as this is, it cannot be avoided. It is a question of allowing the patient to die from stasis, or prolonging life at the expense of inanition and hydremia. Consequently when the system is being drained by these diuretic and cathartic drugs, the effects upon nutrition must be offset so far as possible by simple, nourishing food, iron, arsenic, etc.

Another reason for the exhibition of cathartics, at least early in the

fight against myocardial incompetence, lies in their ability to lessen hypertension. It is often surprising to witness the relief from dyspnœa and pain experienced after a sharp purge. When this alone is the effect desired, a mercurial followed by a saline is the best, and it does not require frequent repetition. This must be governed by the degree of tension and the character of the symptoms. On the other hand, constipation should never be permitted, since it raises the tension of the pulse and induces injurious straining at stool. A moderate amount of saline daily and a calomel purge, occasionally, is advisable in most cases.

Morphine and Heroin.—There is no single remedy of more signal benefit than either of these two therapeutic agents when properly used. If a patient with myocardial incompetence is suffering from smothering attacks which rob him of sleep and compel him to sit up the greater part of the night, surprising relief is usually afforded by a hypodermic injection of a small dose of morphine; $\frac{1}{8}$ grain is better than $\frac{1}{4}$ grain, since it will stimulate the heart and prevent the dyspnœa. In most instances it also induces refreshing sleep. The effect of the morphine is enhanced by the addition of $\frac{1}{200}$ grain of atropine. If a saline cathartic is administered every morning, no unpleasant gastric effects are experienced, and the morphine may be injected in the same dose for a period of days or even weeks without harm. In some patients morphine does not allay the attacks of nocturnal dyspnœa, and heroin may be tried; $\frac{1}{12}$ grain (0.005 gm.) can be given hypodermically at night.

It not infrequently happens that the physician is called to treat one of these sufferers after the stage of profound inadequacy has been reached. The heart is greatly dilated and arhythmic, the legs are œdematous, the liver and lungs are congested, and the patient is unable to lie down because of dyspnœa. Under such conditions digitalis is really worse than useless; besides, it has probably been tried and found wanting. The plan of management which has proved most efficient is a dose of morphine at bedtime, a sharp purge by elaterine or salts to lessen stasis in the lungs and abdomen; $\frac{1}{60}$ grain of strychnine and 1 grain of caffeine, each hypodermically four times a day, and milk diet for twenty-four to forty-eight hours according to circumstances.

By a sharp purge is meant not two or three fluid stools of six to eight ounces each, but a dozen profuse washing passages which remove several quarts of water. Then for several successive days the bowels are kept freely open, until the abdomen is soft and the liver no longer tender. When it is found that the heart has become reduced in size, slower and stronger in action, a careful trial of digitalis may be made.

Venesection.—Undoubtedly there are many cases in which the letting of 20 to 30 ounces of blood proves a very timely measure and starts the patient on his uphill journey. When arterial tension is so high and the pulse so bounding as to congest the head and threaten apoplexy, a vein may be opened and 16 to 20 ounces of blood be abstracted with immense benefit. Nature sometimes gives a hint in this direction by the production of severe epistaxis.

Nourishment.—The heart being an organ that is required to perform almost incessant work, must receive adequate nourishment if it is not

to suffer in its integrity. Nevertheless, the digestive disturbances resulting from circulatory embarrassment often occasion so much discomfort, if not actual repugnance for or positive inability to consume food, that the nourishment of the individual and the selection of food become matters of great difficulty. It is generally held that the dietary should be rich in proteins, and within certain limits such is undoubtedly the case. Moreover, articles of animal origin are likely to be digested with less distress from gas than are cereals and vegetables rich in carbohydrates. But whatever be the form of food selected, it should not be in large amounts.

Digestion is apt to be slow and absorption less rapid than in healthy persons without hepatic and gastric stasis. Consequently, it is a good rule not to administer food at very short intervals. Likewise the intake of fluids should be restricted, especially when there is dropsy and attempts at its removal are being made. Milk may be very serviceable in some cases, and it may be wise to confine patients with abnormal pulse tension to an exclusive milk diet for a few days until the pressure has been reduced. Coffee and tea should be allowed, but sparingly. In some cases, particularly if the individual has been accustomed to wine or strong beverages, it is a good plan to allow a small quantity of such liquids. They not only improve appetite and digestion, but serve as positive nourishment to weak hearts when taken in limited amounts, and particularly with meals. The foregoing suggestions must be modified in cases showing abnormally high or rather excessive blood pressure. In addition to what has been said concerning the desirability of reducing the intake of foods rich in purin bases it may be repeated here that broths and other strong meat soups, butcher meats, salty fish, and coffee are articles all coming under this class.

NEW GROWTHS AND PARASITES IN THE MYOCARDIUM

1. **Syphilis.—Etiology.**—The *Spirochæta pallida* is believed to display a predilection for the cardiovascular system. Although cardiac lues is considered a late manifestation, declaring itself years after the initial sore, still cases have been reported of death from rupture of an aortic aneurism or of an aneurismal dilatation of one of the sinuses of Valsalva within a few months after the chancre. Although cardiac syphilis may be congenital it occurs far most often in adults. It is said to exist more often in the male sex, although females are by no means exempt.

Morbid Anatomy.—This disease may give rise to changes of a chronic nature in any of the cardiac structures, but the endocardium is the least likely to be affected. In the aorta it appears as a mesaortitis which leads to aneurism or to aortic regurgitation with but moderate dilatation of the vessel. In such instances the aortic valves are quite likely to display changes due to cellular infiltration and thickening, while the adjacent endocardium may show slight degenerative change of a yellowish color. In the heart wall the disease is said to appear generally either as a sclerotic process or as gummata. Warthin has demonstrated areas of fatty degeneration in which areas the spirochete

was identified. He believes, therefore, that fatty degeneration of the myocardium is more often syphilitic than has been thought hitherto. Fibrous thickening of the endocardium or pericardium may be associated with the process in the myocardium. The sclerotic form of cardiac lues is said to be more frequent than gummata and affects chiefly the wall of the left ventricle, appearing as circumscribed patches of fibrosis.

The coronary arteries generally display the changes of obliterative endarteritis, that is, cellular infiltration and thickening of the subendothelial layers and consequent obliteration of the lumen. Osler states that gummatous peri-arteritis may affect the coronaries as well as the arteries of the brain, although less frequently. This is the only form of arteritis which can be regarded as specific. Should the endarteritis obliterans of Heubner be found in association with syphilitic lesions in other parts of the heart, or other organs, its luetic nature may be regarded as assured.

Gummata in the heart wall are comparatively rare. The tumors may be recent, or old and single or multiple; the gumma appears as a soft, grayish mass of variable size surrounded by a capsule of fibrous tissue. Old gummata are dry, caseous, and yellowish white. The pericardium overlying the gumma is usually seen to be thickened but seldom adherent. There may also be outgrowths upon the valves, as reported by Janeway and others, in association with gummata in the myocardium.

Symptoms.—Except in cases in which mesaortitis has led to aneurism or aortic regurgitation, heart syphilis is far less often recognized clinically than postmortem. The explanation lies in the fact that it is quite apt to remain entirely latent. Even when symptoms are produced, they do not present features that may be considered characteristic or distinctive. *Tachycardia* and *arhythmia* have been emphasized by Semmola. They may occur alone or together, but to be significant must be independent of any other discoverable cause, as dilatation or valvular disease. In a case reported by Ashton, Norris and Lavenson, there was bradycardia with convulsive seizures and other features of the Stokes-Adams syndrome; after death from heart-block, a gumma was found in the interventricular septum involving the bundle of His. *Precordial* pain of an indescribable or dull character, or of the nature of a vague distress rather than actual pain, has likewise been described. *Angina pectoris* also has been noted, and when occurring in a person under forty-five years of age, is very suggestive of coronary sclerosis due to syphilis.

Examination of the heart may or may not reveal signs of disease. There may be appreciable enlargement, or on careful percussion its area of dulness may appear entirely normal. This latter is one of the points on which Runeberg lays stress in connection with suspicious symptoms. Not infrequently the tones are clear but Runeberg has observed a muffling or tonelessness of the first sound at the apex.

Diagnosis.—Except in cases characterized by signs of involvement of aorta and valves this must be inferential or problematical. The occurrence of some of the symptoms mentioned in an individual furnishing evidence of syphilis in other parts would render the diagnosis reasonably certain. In most cases the diagnosis must be established by history and exclusion rather than direct evidence. Tachycardia and arhythmia,

without obvious signs of disease in heart or bloodvessels, and to account for which no disturbing factors can be discovered in other organs, is, according to Semmola, good and sufficient ground for a trial of antisyphilitic medication. The development of angina pectoris in a man under forty-five may also be considered of luetic origin, provided no other satisfactory cause can be determined. The Wassermann reaction is of great value.

Prognosis.—This may be said to be good, provided treatment is instituted before the development of irremovable changes. When unrecognized and, therefore, untreated, it is likely to lead to a fatal termination in the course of time. Extensive coronary sclerosis is very likely to terminate in sudden and unexpected death. Accordingly, the development of anginal seizures of this origin possesses a very grave significance and renders the individual wholly uncertain of his life.

Treatment.—This must of course be antisyphilitic (salvarsan and mercury) in the hope of arresting or removing the changes. To be efficient, the remedies should be pushed to the limit of toleration and ought to be continued for some time after the cessation of symptoms. In particular the heart should be spared from strain during the course of specific treatment and the individual's general health receive close attention. Salvarsan intravenously is not devoid of danger and hence this remedy should be used with caution.

2. **Tuberculosis.—Etiology.**—Tubercles occur in the myocardium with tuberculous pericarditis and in general miliary tuberculosis.

Morbid Anatomy.—This possesses greater pathological than clinical interest. The disease may be discovered as miliary nodules scattered through the myocardium, as caseous masses or as a diffuse sclerotic process. The tubercles are said to be discovered especially in the sulci along the linè of the vessels. Caseous tubercles are exceedingly rare, while the sclerosis of tuberculous origin presents no features that distinguish it from the same process of other causation.

Symptoms.—If such are produced they are obscured by those of the tuberculous infection in general. The invasion of the heart is said to occur chiefly in acute cases, and hence any rapidity or feebleness of the heart's action that may be observed is likely to be attributed to the asthenia and pyrexia of the primary affection.

Diagnosis.—This can be made with certainty only postmortem.

Prognosis.—This is in reality that of the primary infection. It probably exerts but little influence on the course of the malady.

Treatment.—This includes the administration of digitalis, etc., if cardiac asthenia becomes pronounced.

3. **Blastomycosis.**—Another of the rarities of medicine is the dissemination of blastomycotic granules in the myocardium. They occur as a part of generalized blastomycosis, of which some seven undoubted instances have been reported. In the case recorded by Clary[1] the fungi were discovered in the myocardium as an accidental finding of the postmortem. The heart weighed 180 grams and scattered through the

[1] *Transactions of the Chicago Pathological Society*, 1904, vol. vi.

heart walls were miliary nodules resembling those of tuberculosis. The clinical picture in this case was that of chronic nephritis. Blastomycosis of the heart possesses no clinical interest, since it is secondary and but a part of the generalized disease, and can only be surmised, not diagnosed, during life. It is doubtful if it materially influences the prognosis, which, to judge from reports, is absolutely hopeless.

4. **Actinomycosis.**—It will probably surprise the reader to learn that actinomycosis of the myocardium is more frequent than is either syphilis or tuberculosis in this situation. Such at all events is the statement made by Hektoen. Perhaps the results of the Wassermann test and Warthin's recent contributions to cardiac syphilis made since the foregoing statement by Hektoen would modify the latter's declaration. Any portion of the circulatory system may be attacked, but the endocardium would appear to be involved rather less frequently than the pericardium or heart wall, and then in consequence of encroachment of a myocardial process upon the cavities of the organ.

Etiology.—The invasion of the heart may be by direct extension, or by the blood stream. Involvement through the lymphatics has not yet been demonstrated. The metastatic form is stated to be the more common, which is not surprising when one understands the frequency with which actinomycotic masses are found projecting into the interior of the veins in various parts. When the process has extended from the lungs or other adjacent structures, there are generally dense fibrous adhesions binding together the various tissues.

Morbid Anatomy.—Actinomycotic granules within the myocardium vary much in number and size. They have been found in all portions, including the auricles and papillary muscles. These foci are more often metastatic in origin and hence may be either single or multiple. Their size is also not constant, but the majority range between 1 and 4 cm. in the greatest diameter. The largest mass on record is that of Ponfick, which was a yellowish nodular mass, of the size of an apple, situated in the wall of the right heart at the level of the auriculoventricular opening.

Foci of myocardial actinomycosis are very apt to set up either circumscribed or diffuse pericarditis, which may be exudative or fibrous. The exudate may be fibrinous or serofibrinous, and in some instances purulent. Not infrequently this exudate is found to contain the characteristic sulphur granules of the actinomycotic fungi.

Symptoms.—These are apt to be obscured by those of the process in the lungs or other parts. They will depend upon the character of the changes that have taken place in the pericardium or elsewhere.

Diagnosis.—This can only be surmised, not definitely determined. The appearance of cardiac incompetence or signs of pericarditis, in a person suffering from actinomycosis, would render probable the involvement of the cardiac structures and, therefore, of the heart walls.

Prognosis.—This is hopeless.

5. **New Growths.**—These are both relatively and absolutely very rare in the heart. They may be of any kind, although some occur more often than others. The variety of heart tumors is shown by Berthenson's figures, who, out of 30 instances found 9 of sarcoma, 7 of myoma, 6 of

fibroma, 2 of gumma, and 3 each of carcinoma and cystic tumors. Of these the cardiac cavities were invaded in 22 cases (Wittaker) as follows: right auricle 7 times, right ventricle 3 times, left auricle 7 times, and left ventricle 5 times. Lipoma and myxoma have also been met, but are still more uncommon than the forms already mentioned.

Malignant neoplasms possess the greatest interest to the clinican, since they are the most serious. Although too many have been reported to make them a clinical curiosity, still their absolute infrequency is shown by the fact that up to 1893, Tedeschi was able to find only about 80 cases in the literature. To these he added 3 of his own, and as others have been recorded since his paper appeared, it may be quite safely stated that the total number to date will fall not far short of 100. Carcinoma is more frequent than sarcoma, and yet the relative rarity of cancer of the heart is shown by the following figures: Koehler found but 6 instances among 9118 autopsies, Fanchon 6 in 8189 autopsies, Willigk 9 of the heart and 7 of the pericardium in 4547 autopsies. The infrequency of cardiac cancer may be still further judged by the fact that Willigk's 16 instances occurred among 477 cases of the disease in general. When we come to consider the two forms of primary and secondary cancer of the heart, primary cancer is by far the less frequent. Thus, Petit is said to have found but 7 instances in the literature.

Etiology.—Malignant growths in the myocardium are very rarely primary. The neoplasm is most commonly secondary to disease of the mediastinum or lung, but may be metastatic from distant parts. In some instances the growth invades the heart by direct extension. The disease may occur at any age, even in childhood, but is of course most frequent in middle age.

Pathology.—Malignant neoplasms, whether carcinoma or sarcoma, are usually secondary to malignant disease of neighboring or distant parts. They may occur in the heart as either a single growth or as multiple nodules, more often the latter. The disease seems to be situated rather more commonly in the right side of the heart, especially when it is metastatic. In not a few instances the growths invade both the pericardium and myocardium, and it is often difficult to decide in which of these two situations the disease is primary. The presence of multiple nodules throughout the heart causes great enlargement of the organ, and the pericardium may be filled with a bloody exudate in consequence of the invasion of the sac. The tumor may obstruct the orifice near which it is situated, and, if the mass projects into the cavity, the endocardium overlying it may be eroded. As the cancer is most often of the colloid variety it is likely to give rise to metastases, and the pulmonary artery may be occupied by carcinomatous emboli, as in Osler's case.

Symptoms.—There is nothing characteristic. There may be evidences of heart weakness, the pulse may be accelerated and irregular; but as the location in the heart is usually secondary to disease of other structures, these symptoms may be attributed equally well to that fact. Precordial pain has been noted, and in such cases is probably to be referred to pericardial involvement. Distension of the pericardium, with sanguineous fluid, is shown by the usual signs of pericardial exudate.

Diagnosis.—This is either impossible or a matter of good fortune. It is extremely doubtful if primary cancer of the heart can ever be diagnosed with certainty, and except in unusually favorable cases even the secondary form must be inferred rather than determined with positiveness. Involvement of the myocardium may be surmised upon the development of cardiac symptoms, that are more severe or of another character than can be readily explained by mere weakness on the part of the patient; likewise, if precordial dulness becomes so increased as to point to distension of the pericardium with fluid, or if signs be detected which indicate obstruction of an orifice or leakage of a valve.

Prognosis.—This is absolutely hopeless.

Treatment.—This is limited to the relief of symptoms and the sustaining of heart power.

6. **Echinococcus.**—This is a very rare occurrence in the myocardium. Of 1862 cases of hydatids, comprised in the united statistics of Davaine, Cobbold, Finsen, and Neisser, there were but 61 instances in which the heart and bloodvessels were the seat of disease.

Etiology.—Echinococcus disease of the heart may be primary, but is usually secondary to hydatids in other parts. In either event the parasites are conveyed to the heart in the blood stream.

Pathology.—Echinococcus cyst of the heart may be either intramural or endocardial, and may vary in size from that of a bean to that of an orange. The number of the hydatids also varies much. There may be but a single cyst situated in the myocardium, or there may be many cysts occupying and completely filling a cavity. When in the interior of the heart the cysts may be loose or pedunculated.

Symptoms.—These depend upon the seat of the cysts, whether in the wall or a cavity of the heart. They cannot be predicated, therefore, and indeed are probably disguised by signs pertaining to the disease in other organs. The fact of sudden death from blocking of a pulmonary artery by cysts in Crowther's case should be kept in mind, as well as the possibility of pulmonary echinococcus resulting from rupture of a primary hydatid of the myocardium, as in Grulee's patient. One should also remember that serious obstruction to the circulation may result from cysts situated in the interior of the heart.

Diagnosis.—This can only be inferred when, in an individual known to have echinococcus disease of the liver or other viscera, symptoms arise which point to possible implication of the heart.

Prognosis.—This depends largely upon the seat and subsequent history of the cyst. Its rupture may cause death, or be responsible for a secondary invasion of the lungs through which the life of the individual ultimately may be sacrificed. In most instances death is likely to occur, either directly or indirectly, through the cardiac disease.

Treatment.—This must be purely symptomatic.

CHAPTER V.

ACUTE ENDOCARDITIS.

By Sir WILLIAM OSLER, Bart., M.D., F.R.S.

Definition.—Acute inflammation of the lining membrane of the heart and its valves, an incident in an infection or a terminal event in some chronic disease, is characterized anatomically by vegetations, necrosis, and ulceration. Chronic endocarditis, which may be either a primary change or a sequence of the acute process, will be discussed with chronic valvular disease of the heart.

Classification of Forms.—According to the *nature of the infecting agent* we speak of streptococcic, staphylococcic, pneumococcic, rheumatic, typhoid, or gonococcic; according to *the character of the lesion*, of verrucose or ulcerative; according to the *severity of the symptoms*, of benign and malignant varieties.

There is always a lesion of tissue—erosion of endothelium, vegetative outgrowths, ulceration—and the danger depends, first, on the nature of the infecting agent; secondly, on the extent of loss of substance, and thirdly, on the state of the body, *i. e.*, blood defences. But in any case there is no *benign* or *simple* form. Endocarditis is always a serious lesion, if not immediately by loss of substance, etc., remotely by the sclerotic changes which lead in a majority of the cases to retraction and insufficiency of the valve. The so-called benign endocarditis kills in the long run a very much larger number of persons than the malignant form. Nor is the term acute free from difficulties. Infectious endocarditis is usually an incident in some acute infection, and the duration is reckoned by weeks or by a few months, and yet there are cases in which the process is active and symptom-producing for eight, ten, twelve, or more months—an essentially chronic condition.

There are clinically four great groups of infective endocarditis:

I. The *simple* endocarditis of the general infections (rheumatic fever, scarlet fever, typhoid fever, etc.), and, as a terminal infection, of many constitutional disorders. In itself, as a rule, harmless at the time, it leads in many cases to sclerosis of the valves and to chronic heart disease.

II. The *ulcerative*—the lesion is part of a septicopyemia arising in a local infection, a skin wound, the puerperal process, an acute bone disease, gonorrhœa, etc.; less often in septic processes without external lesion, as in pneumonia. The endocarditis is only an incident, although often a serious one, in the infection.

III. The *recurrent* endocarditis on the old sclerotic valves of chronic heart disease, a common form, which may be slight or severe.

IV. *Chronic septic* endocarditis, in which for many months a state with remittent or intermittent fever is caused by the growth of vegetations on the valves.

In groups I and II the symptoms are part of an infection in which the endocarditis is an incident. In III and IV the symptoms are directly due to the focus of infection on the valves.

General Pathology.—The following statements formulate our existing knowledge:

1. Infective endocarditis is a valvular or mural lesion, and on the valves the closure lines are points of election, viz., on the aortic cusps a little below the free edge and on the auriculoventricular valves the auricular face, a little distance from the margin. In the fetus the right heart is most frequently affected, in the adult the left. Malformations, as, for example, the edge of an imperforate septum, and valves which have sclerotic changes are especially prone to be attacked.

2. Most frequently an incident in septicemia, it is not always possible to say whence the infection has been derived. In almost any one of the ordinary febrile diseases endocarditis may be a complication, but it is particularly during childhood that we meet with it, and above all others in the rheumatic affections. The tonsils are probably the portals of entry for the microörganisms in this group, and also in the not infrequent cases of endocarditis without recognizable cause.

3. Certain bacteria are much more prone to excite endocarditis than others. The streptococci and staphylococci (with which may be included provisionally the "micrococcus rheumaticus"), the pneumococcus, and the gonococcus, are the chief endocarditis-producing organisms. A definite group of cases has been collected by Libman[1] which are due to what he terms the "endocarditic" coccus, which in some cases corresponds to the *Streptococcus viridans* of Schottmüller. It is a diplococcus which has affinities on the one hand to the pneumococcus and on the other hand to *Streptococcus brevis* as frequently found in the mouth. Its characters are fairly stable, but by the method of passage it has been transformed into one or other of these original types. It gives rise to a definite clinical picture with constant pathological changes (*q. v.*). The typhoid bacillus, the tubercle bacillus, the organisms of plague, cholera, influenza, smallpox, typhus fever, measles, scarlet fever, dysentery, glanders, and Malta fever are much less prone to affect the valves. Even in an acute infection, typhoid fever, for example, endocarditis may be a secondary infection with streptococci or staphylococci. So far as we know, the protozoa do not themselves excite an endocarditis.

4. The liability to infection of the valves does not depend upon (*a*) the number of organisms circulating in the blood. In typhoid fever, in lobar pneumonia, in certain cases of septicemia, there may be the most intense blood infection for weeks without endocarditis. (*b*) Virulence of the organism plays an important part. The most intense local infections are met with in the virulent septicemias, gonorrhœa, etc. (*c*) The bacteria of certain diseases excite only the mildest type of the disease. In rheumatic fever and in chorea the local lesion is itself trifling and rarely associated with destructive changes in the valves. And yet these are the very organisms which have a special predilection for the cardiac

[1] Libman, XVIIth International Congress of Medicine, Lond., 1913.

valves. (*d*) We do not know what determines the settlement of the organisms on special valves or on special portions.

5. Experimental lesions of the valves if made with proper precautions are not followed by endocarditis, but if done with unclean instruments, or if after the injury cultures of suitable organisms are injected into the blood, an inflammation follows. The injection of cultures alone is, as a rule, negative so far as the valves are concerned; but Poynton and Paine, Cole, Rosenow, and others have shown that endocarditis may be caused by the injection of organisms belonging to the streptococcus class and the one which is believed to be the excitant of rheumatic fever. Ribbert has shown that by injecting staphylococcus emulsion containing coarse potato particles, the mitral and tricuspid valves, but not the aortic, are affected. He thinks that the fine particles injure the endothelium at the lines of contact and permit the micrococci to gain entrance, or they may be forced in by pressure.

6. While the general belief is that the microörganisms settle directly upon the valves from the blood current, Koster suggested that the peculiar localization of the lesion might be due to embolism. From the vascularization of the valves this does not seem very likely, although Orth and Wyler suggest that in certain cases of recurring endocarditis in an old sclerotic valve it might be possible, as they contain many large and wide vessels.

7. Strain and tension have a definite importance in connection with endocarditis. The more common involvement of the mitral and aortic valves in extra-uterine life may here find its explanation, and the more frequent implication of the large anterior segment of the mitral. The aortic segments are of practically the same texture, etc., as the pulmonic, but they show much earlier signs of wear and tear in the form of slight thickenings and atheromatous changes. The lines of election on both the arterial and the atrioventricular valves correspond to the very points which bear the greatest strain and on which, if anywhere, the endothelium would first suffer.

Morbid Anatomy.—In addition to changes in the endocardium there are usually alterations in the myocardium and very often in distant organs. The endocardial lesions are three—verrucose vegetations, necrosis and ulceration, and proliferative changes leading to sclerosis—and to these three correspond the triple clinical picture, the slight symptoms of the simple form, the malignant endocarditis, and the chronic valvular lesion.

1. **Verrucose Endocarditis.**—The lesion is usually in the left heart, and more often on the mitral than on the aortic segments. The peculiar localization has already been discussed. The mural endocardium may be involved but rarely without that of the valves. The vegetations form small, bead-like structures, soft and of a grayish-white color; in other instances they are warty or cauliflower-shaped excrescences, sometimes pedunculated. The smallest vegetation consists of (*a*) blood plates, (*b*) fibrin seated upon (*c*) an endothelium which presents changes. Beneath some of the tiny vegetations the endothelium may appear normal, but, as a rule, it shows signs of proliferation. In stained sections

microörganisms are usually, but not always, found. In a later stage at the site of attachment and in the neighborhood the fixed cells of the subendothelium show proliferation, but there is rarely any leukocytic infiltration. The cells grow into the thrombi, which gradually become organized, hyaline changes occur, and a small, nodular thickening is left. This is the common thrombo-endocarditis which we meet with in so many of the acute infections and in the bodies of persons dead of tuberculosis, cancer, etc. Probably microörganisms are always present. In the more intense forms of the disease, such as that which complicates rheumatic fever, the necrosis of the endothelium is more extensive, the vegetations much larger, and the reaction in the valve tissues much more severe. There is a striking difference in the histological picture of a *bead* of vegetation on, say, the mitral valve in a case of diabetes and the section of a *warty* vegetation in a case of rheumatic fever or chorea in a child. In the one there may be scarcely any tissue reaction; in the other the valve changes are intense. And herein lies the great danger in this form of endocarditis, since in direct proportion to their extent and activity is the liability to the secondary progressive tissue changes in the valve leading to contraction, thickening, and insufficiency. On valves affected in this way verrucose endocarditis is very common, and presents two peculiarities—the vegetations show more rapid changes, as the vascularization of the valve is greater, and there is a greater danger of widespread necrosis and ulceration.

2. **Ulcerative, Vegetative, and Necrotic Lesions.**—Both sides of the heart may be affected, the right in larger proportion than in simple endocarditis. Of 209 cases, aortic and mitral valves were affected together in 41, aortic valves alone in 53, mitral valves alone in 77, tricuspid in 19, pulmonary valves in 15, heart walls in 33, and in 9 cases the valves of the right side of the heart were affected alone. Macroscopically there are three types of lesions: (*a*) Ulcerative, causing extensive destruction of the endocardium, of the texture of the valve, or even forming a deep ulcer which may perforate the aortic ring or the septum. Often it is only a superficial erosion of the valve covered with a gray, diphtheritic-looking membrane, hence the term diphtheritic applied to this form; or an aortic or mitral cusp may be perforated or a valve aneurism is formed. The most extensive destruction may occur, or a segment is eroded completely; in one instance two of the aortic cusps had completely disappeared to the line of attachment, which was smooth, while the third segment was more than half destroyed. In some of these severe ulcerative forms there are very few vegetations. When upon the base of a mitral leaflet or near the aortic or pulmonic ring the lesion may be deep and destructive, forming what is called acute perforative ulcer of the heart. This type is most frequently the result of infection with streptococci or other pus organisms. The process may be very acute; in a case in which a large ulcer penetrated deeply into the muscular substance below the aortic ring the entire illness was within ten days. Septic emboli, hemorrhage, and suppuration are frequent with this form. On the other hand, it may last several months and without acute symptoms.

(*b*) Globose, grayish-yellow, or greenish-gray vegetations projecting from the valves, often having a fungoid aspect and without much superficial ulceration, but with great necrotic destruction of valve tissue, leading frequently to perforation. Seen in pneumonia and in gonorrhœa this type is common, and while there may be high fever and septic features, emboli and hemorrhages are not so frequent. When of any duration, the vegetations are not infrequently encrusted with lime salts. The process may extend beyond the valves. In one case there were mycotic aneurisms of the aorta, while in another they extended along the pulmonary artery almost to the hilus of the lung.

(*c*) A proliferative form characterized by outgrowths from the valves, the chordæ tendineæ, and the mural endocardium. In all varieties vegetations occur, but in certain of the severer infections they are larger and the valves are encrusted with firm, yellowish masses, often hanging in tags from their edges or coating the chordæ tendineæ, some of which may be eroded through. The mitral orifice may resemble the mouth of a miniature cave surrounded with stalactites, and the tendinous cords resemble twigs encrusted with lime salts. They are solid structures, not friable, intimately united with the endocardium, and the whole thickness of the valve may be involved at the attachment. In long-standing cases the vegetations may be very large, dry, hard, yellow, and without adherent thrombi.

(*d*) The form previously referred to as being produced by Libman's endocarditic coccus produces moderate, rigid, warty growths on the mitral or aortic valves or on both, but whichever valve it affects it tends to spread in the case of the mitral valve on to the posterior wall of the auricle, and from the aortic valve it spreads to the ventricular endocardium and the ventricular aspect of the mitral valve. The chief characteristic of this type of lesion is that in certain cases it becomes completely healed. The patients have fever, anemia, petechial hemorrhages, tender nodules in the skin of the hands and feet, slight renal hemorrhage, and frequently a large spleen. The duration of the illness is usually from four to eighteen months and is almost always fatal though not always from the cardiac changes. The kidney shows characteristic changes in the glomeruli, and the patients may die either early or late from renal complications. Calcification of the vegetations and softening may lead to embolic brain symptoms.

Etiology.—Portals of Entry of the Infection.—Practically in all cases the microörganisms gain entrance through the skin or mucous membranes. In the important group of cases in which the endocarditis is secondary to bone lesions the primary source of the infection, although often obscure, has been through one or other of these channels.

Mucous Membrane.—(*a*) *Alimentary Canal.*—This is the most common portal of infection. In the mouth alveolar abscess and the necrotic changes associated with bad teeth are occasional causes. Pyorrhœa alveolaris, an almost universal malady after middle age, is rarely a cause of endocarditis. Possibly some of the unexplained cases may be due to it. The *tonsils*, the mycotic hot beds, are responsible for a great many cases, and if, as is now commonly believed, the infection of rheu-

matic fever is here nurtured, they take the first rank as sources of infection. Certainly from them may be cultivated at any time the very organisms most prone to excite endocarditis. Not many cases are met with in connection with affections of the œsophagus or stomach. Ulceration of the intestines, typhoid, tuberculous, or dysenteric, may be complicated with endocarditis. A very important group occurs in connection with infections of the bile passages. Appendicitis is a rare cause.

(*b*) *Genito-urinary.*—Gonorrhœa, abscess of the prostate, chronic cystitis, and suppurative processes in the kidneys are common sources. Postpartum infection contributes an important group of cases.

(*c*) *Respiratory Tract.*—Among primary foci may be mentioned suppuration in the nose and adjacent sinuses, affections of the larynx and trachea, and occasionally bronchiectasis. Infection of the valves is a common complication of pneumonia, while pleural suppuration is a rare cause.

Skin.—Many of the severest forms follow local skin infections—postmortem wounds, an accidental cut or prick during an operation, or the most trivial trauma may be the portal of entry. As a rule, in these severe infections following skin lesions, the endocarditis plays a secondary part. The picture is that of an intense septicemia. The primary wound may be slight and may have healed before the severe symptoms are manifested. The writer saw such an instance in 1903, and although endocarditis was suspected and the blood was for weeks swarming with organisms, there were no physical signs to indicate the extensive lesions found postmortem. Many of the worst cases are in association with these comparatively slight infections of the fingers, as in one remarkable instance, in which a stalwart young fellow with an old mitral lesion, following the cleansing and cutting of his nails by a "manicure," had paronychia, which excited a malignant endocarditis, of which he died. Erysipelas may be complicated with severe endocarditis.

Primary Endocarditis.—A primary endocarditis the result of injury or of cold has been described. It is not always possible to determine that the valve lesion is really secondary. In one of the most acute cases of ulcerative endocarditis in the writer's series no primary source of infection was found, but the tonsils were not examined, and it is not possible to exclude all foci. A small spot of necrosis of the jaw, an insignificant joint lesion in a child, a small area of bronchopneumonia, a prostatic abscess the size of a pea, may be the source. The so-called endocarditis from cold is probably always rheumatic and of tonsillar origin, and it may occur in the febrile attacks of children as the result of slight and even overlooked tonsillitis.

Practically all cases of endocarditis may be regarded as secondary to an existing infection.

Endocarditis as a Terminal Infection.—In the hearts of persons dead of chronic affections of all sorts—tuberculosis, dysentery, gout, cancer, chronic nephritis, arteriosclerosis, diabetes, chronic affections of the nervous system—it is common to find on the mitral valves, less often on the aortic, tiny beads of vegetation festooning the segments in the usual situation. In these very small soft structures it is not always

easy to determine the presence of microörganisms. This is the mildest form of terminal infection, as the endocarditis rarely produces any symptoms, and is never responsible for the final event.

Rheumatic Infections.—All other causes sink into insignificance before the endocarditis-producing poison of this motley group. The researches described by Poynton in the article upon "Rheumatic Fever"[1] have brought us nearer the solution of one of the most important problems in pathology. The precise germ may not yet have been settled, but the evidence suggests that the group of disorders to which the name rheumatic is applied depends upon infection with organisms related to the streptococcus group. The examination of the vegetations in rheumatic affections has been made in many cases, and a variety of organisms has been described.[2] The reader is referred to the section by Poynton for a description of the organisms which have been found.

Portal of Entry of the Germs.—Opinion has centred of late years upon the tonsils as the chief source of the infection for the following reasons: (*a*) The widespread, almost universal involvement of these structures in young children; (*b*) the demonstration in them of the very organisms which have been isolated from the lesions of rheumatic fever; (*c*) the clinical association of tonsillitis and arthritis; (*d*) the frequency of tonsillitis as a link in the rheumatic chain in young children; (*e*) the beneficial results which have followed removal of these structures in persons subject to recurring attacks of arthritis. There are still many points to be carefully considered. Tonsillar infection is universal in childhood, while rheumatic infection, although common, only occurs in a comparatively small proportion of children. But the same holds good with many "facultative" infections which we carry about. Only a few get pneumonia of those who harbor the pneumococci; not all take typhoid fever who carry the bacilli; many have foci of tuberculosis who never become tuberculous, and it is quite possible that in the tonsils, the crypts of which are natural culture tubes, many harbor the germs of the rheumatic affections of whom only a few show the positive manifestations. Invasion is a question of lessened resistance, lowered phagocytic power. Localization, whether in the joints, the nervous system, the skin or elsewhere, depends on circumstances of which we are as yet profoundly ignorant; and the same must be confessed of the precise circumstances which determine the occurrence of endocarditis in any individual case. With the following infections belonging to the rheumatic group endocarditis may be associated:

(*a*) *Tonsillitis.*—Many writers have called attention to the presence of valvulitis in this affection, particularly Haig-Brown[3] and the much lamented F. A. Packard.[4] It may not be possible to determine definitely the nature of a given attack of tonsillitis. The lesion may be slight and readily overlooked, or there may be nothing more than a diffuse reddening with œdema and relaxation of the fauces. Many of the obscure febrile attacks in children, lasting from five to seven days without any localizing

[1] This work, Vol. I, Chapter XXXI.
[2] See Vol. ii, part i, of the new edition of *Allbutt's System.*
[3] *Lancet*, 1886. [4] *Transactions of Association of American Physicians*, 1899.

features, are associated with a tonsillitis of a very mild character. In such an attack endocarditis may lay the foundation of subsequent valve lesion. And in how many cases of mitral disease, particularly in women, is the history negative so far as the ordinary endocarditis-producing diseases are concerned?

(*b*) *Arthritis.*—Of all manifestations of the rheumatic poison, this is the one with which endocarditis has been recognized as the most serious complication. In children the percentage of valve infection in rheumatic arthritis ranges from 60 to 80, in adults from 25 to 35. Of 360 patients with rheumatic fever, nearly all adults, admitted to the writer's wards at the Johns Hopkins Hospital during fifteen years, 35 per cent. showed organic valvular disease As Bouilland stated in 1840, the rule is for endocarditis, with or without pericarditis, to occur in all cases of severe rheumatic fever. In children the endocarditis may be the chief manifestation of the infection in an arthritis so trifling as to be overlooked, a slight swelling of one ankle, a little redness of one knuckle, with a fever of only a few days' duration. It cannot be too strongly urged upon practitioners to watch with the greatest care every case of joint complaint, however slight, every manifestation, indeed, of obscure fever, in young children, since, as pointed out by Graves, the endocarditis may precede the arthritis.

(*c*) *Chorea.*—Sydenham's chorea is now very generally regarded as an infection very closely related to rheumatic fever. It is not improbable that it will prove to be one of the manifestations of this protean infection. The important point here is that whatever the nature of the poison may be, it is singularly prone to attack the valves of the heart. Some years ago the writer analyzed records of 73 fatal cases of chorea in the literature, and of these 62 had endocarditis. The frequency of this complication has been dwelt upon by all writers on the subject. In Thayer's recent study of 689 cases at the Johns Hopkins Hospital there were 190 cases, or 27.7 per cent., with definite valvular lesions, and in 45 others, murmurs were present. The writer examined 140 children more than two years after the attack of chorea, and found that 72 presented signs of organic heart disease. Arthritis, chorea, and endocarditis form a clinical trio of every-day occurrence in children's hospitals.

(*d*) *Erythema.*—The rheumatic character of nodose and polymorphic erythema has not been demonstrated, but they may be considered here as having at least affinities or relations with the poison which we call rheumatic. The endocarditis which occurs in these conditions is usually simple, but the writer saw one instance of severe endocarditis in a patient with high fever, arthritis, and purpuric urticaria. Many cases of endocarditis in erythema nodosum have been reported by French writers.

(*e*) *Subcutaneous Fibroid Nodules.*—The association of these with endocarditis may be stated: (1) In children they are rarely met with apart from endocarditis. (2) In an immense majority of all cases in children they are a manifestation of the rheumatic poison. (3) They may occur in other than rheumatic forms, and in some of the most extreme cases there has been no arthritis, simply the nodules and a

valvulitis, almost invariably mitral. There are varieties which have a very special relationship with certain forms of endocarditis, and will be referred to later.

Character and Results of the Endocarditis in the Rheumatic Group.—In a majority of instances it is an attenuated virus, producing the common verrucose form, with vegetations a little larger and more cauliflower-like than in the terminal endocarditis. There are four dangers associated with the lesion: (1) A vegetation may break off and cause embolism, a rare event in acute simple endocarditis, more common in the ulcerative form. (2) Recurring endocarditis. Recovery takes place, but fresh crops occur from time to time. (3) Proliferative valvulitis. As already mentioned, the substance of the valve is apt to be involved and the newly formed granulation tissue cicatrizes with puckering, contraction, etc., so that the function of the valve may be damaged very quickly. Within three months of the onset of the illness the leaflets of the mitral may be so curled and folded that not a fourth of their substance remains. (4) Ulceration and destruction of the valve, while not common, occur in a considerable number of cases. There were 24 among the 209 cases analyzed from the literature. Extensive ulceration is a rare event in the endocarditis of childhood.

The special danger, the danger that makes rheumatic fever one of the most serious of all diseases, is the starting of proliferative changes in the valve substance itself, which is gradually followed by cicatrization, with stenosis and insufficiency of the valves.

The Eruptive Fevers.—In *measles* endocarditis is rare, and when it does occur is an incident or a complication, such as bronchopneumonia, and is a streptococcic or pneumococcic infection. In *scarlet fever* it is more common, and occurs in connection with the angina or arthritis. It may be severe and part of an endopericarditis of great intensity. It is rarely of the ulcerative form. In *smallpox*, with such widespread suppuration, one would suppose that endocarditis would be a frequent complication, but it is rare. A systolic murmur at the apex is common as a result of the fever and of the muscular weakness, but it usually disappears. Ulcerative lesions have been described in a few cases, but the simple form is the most common. In chickenpox, mumps, and whooping-cough, endocarditis is not often met with.

Diphtheria.—Both forms have been described, but even in the several types of the disease the valves are not often affected. In 30 autopsies upon cases of a very malignant type the writer found no valve lesions other than the little nodules which seem more common in this than in any other disease. The diphtheria bacillus has been found in the vegetations by W. T. Howard and others, both in the verrucose and the ulcerative form.

Typhoid Fever.—Among 1500 cases there were only 3 with a diagnosis of endocarditis clinically, and among 105 autopsies there were only 3 (a total of 6 in 1500 cases).[1] Typhoid bacilli have been found in the vegetations; clinically the complication is usually without symptoms,

[1] McCrae, this work, vol. i, p. 126.

although in a few instances severe features have indicated the existence of an ulcerative form. It is to be remembered that many of the older cases of typhoid fever with endocarditis were probably cardiac from the outset. In *typhus fever, relapsing fever, cholera, yellow fever, Malta fever,* and *sweating sickness* endocarditis is an occasional complication.

Septicopyemic Processes.—The most intense septicemia may exist without endocarditis; the blood may literally swarm with streptococci or pneumococci for weeks without any affection of the valves. The lesions may be verrucose, but in this group we see the most severe types of ulceration and destruction, with embolic and septic changes in the organs. The infections of this class may be grouped as follows: (*a*) *Erysipelas,* in which the valvulitis may be of either form, but it is not a very frequent complication. (*b*) *Puerpural infections:* Many of the worst cases we meet with follow postpartum septic processes in the uterus or adnexa. Virchow figures a characteristic lesion in his well-known studies upon the subject. It is usually the ulcerative form, and often overlooked clinically in the intensity of the general infection. Eleven per cent. of the 209 instances of malignant endocarditis which the writer analyzed from the literature came in this class. Perhaps more often than in any other condition is the right heart affected. (*c*) Acute bone lesions and osteomyelitis are often complicated by ulcerative endocarditis. The cases are very numerous in the literature. (*d*) *Skin infections,* the septic wounds from whatever source, postmortem cuts or pricks, accidental infection at operation, paring a corn, etc. This is an important group and the endocarditis is usually severe. (*e*) *Miscellaneous infections:* Suppuration in the genito-urinary tract, in the liver and bile passage, abscesses in the abdomen, particularly the old peri-appendicular variety, empyema (rarely), fetid bronchiectasis, a suppurating bronchial gland, a suppurative tonsillitis, etc.

Gonorrhœa.—Only of late years has it been recognized that one of the most common and serious forms of endocarditis was caused by the gonococcus. The valvulitis may be an incident in an early and intense gonorrhœal septicemia, but more commonly it is a complication of the first ten weeks. A few cases have been reported as late as from the third and the fifth month after infection. It has no special relationship with the arthritis. Women are rarely affected; anemia is marked. The aortic, pulmonary, and mitral valves are chiefly affected in this order of frequency. This form is frequently of great severity, associated with high fever, chills, sweats, and hemorrhages, with the embolic features of the most malignant types of endocarditis.

Tuberculosis.—Endocarditis is not very infrequent. It may be (*a*) the terminal thrombo-endocarditis; (*b*) simple, warty endocarditis due to streptococci or staphylococci; (*c*) true tuberculous endocarditis, with tubercle bacilli found in the vegetations which have proved infective to animals. Ulcerative forms are exceedingly rare.

Malaria.—Except as a terminal event in the cachexia, endocarditis is an exceedingly rare complication of this disease. The frequent reference in older writers was due to an error in diagnosis, particularly in connection with the more chronic form of endocarditis associated with

chills and fever. Among the many hundred cases of all forms of the disease studied at the Johns Hopkins Hospital there was not an instance of endocarditis.

Influenza.—A good many cases have been reported clinically, and a few in which anatomically the influenza bacillus has been found in the vegetation, in other instances in association with streptococci or pneumococci.

Symptoms.—A majority of the cases present no symptoms. The terminal endocarditis of the chronic diseases, the slight attacks of many febrile disorders, and even the complicated valvulitis of a septicopyemia may give no indication of their presence, either by subjective sensations or by physical signs. The cases may be considered in three groups—the simple warty endocarditis, the acute ulcerative forms, and the chronic septic endocarditis.

Simple Endocarditis.—Fever is the most important single symptom. As a rule, it is already present in the disease in which the complication occurs, as in rheumatic fever, pneumonia, etc., but with the onset of the valvulitis the temperature rises or changes in character. The terminal thrombo-endocarditis may be afebrile; on the other hand, the slight rise in temperature for a few days before death, not uncommon in chronic nephritis or any protracted illness, may be associated with the occurrence of vegetations in the valves. The recurring endocarditis on the old sclerotic valves of aortic or mitral insufficiency may be indicated only by a slight pyrexia. The old hospital patients with these affections return again and again with slight febrile attacks or with transient cardiac insufficiency and an elevation of temperature for a week or ten days. In several such instances sudden death has occurred, and the only lesion to account for the fever has been the beady valvulitis on the old sclerotic segments.

After all, it is in children that endocarditis is a serious affair—perhaps *the most serious single infection responsible for almost as many deaths as all of the exanthematous affections of childhood together*—and in them fever is *the* symptom. A chill at the onset is very rare. It is not easy, nor always possible, to distinguish the fever of the primary disease from that of the complication, as for example in rheumatic fever, when the disease is at its height, a loud, systolic murmur has appeared under observation. But when the arthritis has subsided and the temperature has fallen a recurrence of the fever alone with the characteristic physical signs is the best indication that valvulitis is present.

So, too, in other affections, *e. g.*, tonsillitis, the same rule holds good. There is nothing characteristic in the fever—a daily rise of from 1° to 3° following the diurnal range. A sweat at night is not uncommon. The temperature may keep above normal for weeks; in fact, there may be nothing but the slight elevation to indicate that anything is the matter.

Does a growth of vegetations on the valves ever take place without fever? Not often in children, although it may be possible; but in adults even the worst types may be afebrile. Headache, loss of appetite, and the usual accompaniments of slight fever may be present. Symptoms

pointing to involvement of the heart are inconstant. There may be no complaint to call attention to this organ. The *pulse* rate is increased with the fever, and in a few instances it becomes small and irregular, but there is nothing suggestive or characteristic. *Pain* about the heart is rarely complained of in the simple form occurring for the first time with rheumatic or other fever, but in the recurring endocarditis of old mitral or aortic disease, pain, even anginal in character, may occur with the febrile paroxysms. More commonly there is slight precordial distress. With pericarditis pain is more frequently met with, but the most severe endocarditis may be latent. *Palpitation* may be complained of, less often in children than in adults, and it may be associated with a transient oppression of breathing or a desire to sit up and take a deep breath. Disturbance of the skin sensations may be present—sensitiveness on pressure about the nipple or in the pectoral fold.

Physical Signs.—Inspection.—In children with fever the heart's action is usually forcible and the pulse is visible in the fourth and fifth interspaces, and in thin chests, even in the third. Much may be gathered from careful inspection of the precordia. The position of the apex beat, the character of the impulse, its extent and nature, indicate the state of the heart wall, and are measures to some extent of the severity of an endocarditis. As already mentioned, the little chaplet of vegetations does not represent the whole affair in endocarditis, but the heart muscle is always affected, weakened by the fever when high and still more by a myocarditis, if present; and these changes are expressed by differences of the impulse and a slight dislocation outward of the apex beat. But it is more particularly with reference to prognosis that inspection is of value. For example, after an attack of rheumatic fever in a child, in whom an apex systolic murmur is present and persists, if when lying recumbent and straight the apex beat is within the nipple line and not forcible, we may feel confident that the damage to the heart is not serious, and even though the murmur persists there is not much if any valvular insufficiency. On the other hand, with the apex beat forcible, in and outside the nipple line, we know that serious damage has occurred and that the organ is crippled. In fact, inspection in heart disease often gives data of more value than those obtained by any other way, as they are less liable to misinterpretation.

Palpation.—Increased force and extent of the impulse are usually present, and the shock of both sounds may be felt. The shock of the second sound may be felt in the second left interspace. A thrill is very rare, but in a violently acting heart during high fever, a vibratory sensation is sometimes to be felt which simulates a thrill.

Percussion.—With involvement of the myocardium and consequent dilatation there is increase in the cardiac dulness, best appreciated by light mediate percussion, upward and to the left. Increase to the right is not so easily determined. In many cases no change is to be determined. The personal equation has to be taken into account, and there are men with deft fingers and keen ears who recognize very slight alterations in the cardiac outlines.

Auscultation.—A majority of cases of acute endocarditis are on the

mitral valves, and the most constant physical sign is the occurrence of a systolic murmur at the apex region. Two circumstances have to be remembered in connection with the diagnosis of endocarditis. In children and young adults with thin chests it is very common to hear a murmur at the second left interspace, which is of no moment whatever, and in fever with a rapidly acting heart a systolic bruit is usually present. The presence of a murmur then is of itself no indication that endocarditis is present, particularly if it is loudest over the body of the heart and at the pulmonic area. The murmur that is of moment in a given case, say rheumatic fever, has the following characters: (*a*) It has come on under observation and may have developed directly from a roughness or blurring of the first sound. (*b*) It is apical, below the fourth rib, often most intense upon it, but is also loud at the apex and is transmitted as far as the midaxillary line. (*c*) Soft and whiffing in quality at first, it may change under observation and become harsher. (*d*) It is present in the recumbent, sitting, and erect postures, often most intense in the first named; and (*e*) lastly, and most important of all, it is permanent. After all the symptoms have gone it persists and may increase in intensity. These are the important features in the simple form of mitral valvulitis met with in the acute infections, particularly in rheumatic fever. It is important to bear in mind that in a considerable proportion of all cases the condition is latent, and it may be accidentally discovered weeks after the original illness that the child has a valve lesion.

Infection of the aortic segments is much less common and, except in adults, is rarely met with alone. It is still more difficult to recognize. A systolic bruit at the base is very common in febrile states, and there is nothing to distinguish the murmur of rapid action and of altered blood states, etc., from that of a valvulitis. Only after convalescence may the persistency of the murmur, the increased vigor of the apex beat, and the slight extension of the cardiac dulness determine the diagnosis.

Simple endocarditis of the valves of the right side of the heart is of rare occurrence and still more rarely recognized.

Termination.—(1) The vegetations may disappear completely and leave no damage. Probably this is the case only with the slighter forms of thrombo-endocarditis, in which it may be shown histologically that there is little or no change in the valve tissue itself. (2) The vegetations themselves may gradually disappear, but the condition has been one of infiltration of the delicate membrane, and there is permanent damage caused by the shrinking and thickening of the tissues in a chronic, progressive valvulitis. (3) The vegetations increase in luxuriance, and the infiltration of the tissue leads to necrosis and ulceration. This is comparatively rare, as in only 24 cases of the writer's series did ulcerative endocarditis occur in rheumatic fever, and which may reasonably be supposed to have followed directly upon the simple form. (4) And, lastly, a fragment of vegetation may be whipped off, with the result of embolism in one of the arteries of the brain, the liver, the spleen, etc.—a comparatively rare event in the simple endocarditis of the fevers, but common enough in the recurring form on old sclerotic valves.

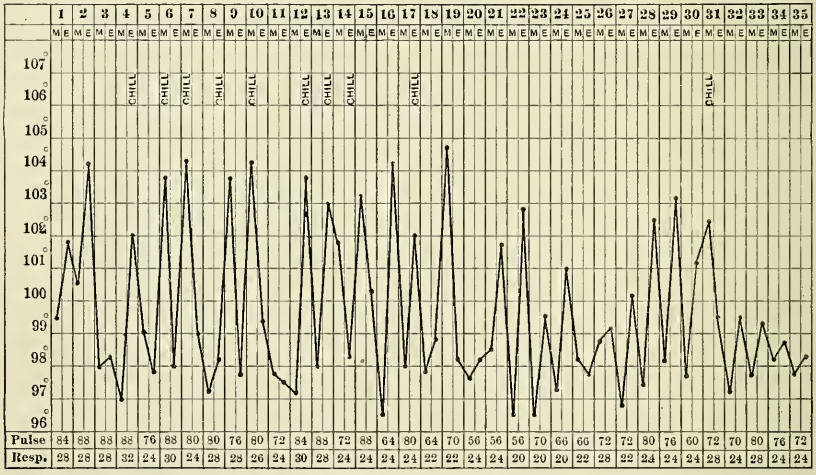
Complications.—Sturges very correctly insisted that a majority of the cases are best described as *carditis*, so frequently are the epicardium and the substance of the heart involved. *Pericarditis* is very common, particularly in rheumatic fever. As a rule, it is readily recognized by the presence of the characteristic rub, and is usually of the simple form without much effusion. *Myocarditis* is practically a constant accompaniment of endocarditis, more particularly the rheumatic form. The feebleness of the pulse, the cardiac irregularity, especially that form which indicates a lesion of the *a-v* bundle, the precordial distress, and the dyspnœa are features associated with this complication. Very rare complications are acute aortitis and rupture of one of the chordæ tendineæ. Of other complications, pleurisy and pneumonia are most common, particularly in the rheumatic cases.

Malignant Endocarditis.—The manifestations are those of septicopyemia; and in a great majority of all the cases the features of the general infection dominate the picture. The clinical features are much influenced by the character of the infecting organism. The pus producers present a picture of severe and rapid pyemia, with chills, fever, suppurative infarcts, and hemorrhages, symptoms which are associated with ulcerative lesions and numerous septic emboli. In the non-suppurative forms, the features, as a rule, are less intense, the cardiac symptoms more marked, and the picture is that of a septicemia, as indicated by high and irregular fever. But there is no end to the diversity of the symptoms, and it does not seem possible to make always a separation between the suppurative and the non-suppurative varieties. Writers have been in the habit of grouping the cases according to the dominance of certain symptoms: (1) *The pyemic form:* In this there is usually the well-marked local infection, but in other instances there is no definite focal lesion. Chills, sweats, high fever, progressive anemia, wasting, with embolic features, such as hemorrhages, bloody urine, pain over the spleen with enlargement of the organ, in some cases blocking of the larger vessels causing hemiplegia, or, in the large arteries of the limbs, gangrene, are the important symptoms. The heart features in this group are very variable. They may be marked—a loud murmur may develop under observation, and increase in intensity, changing in quality, and there are signs of dilatation of the heart. Or, under observation in the course of a few days an aortic diastolic murmur may arise. Under these circumstances, with a local lesion or in a postpartum case the recognition is easy enough. But in another group of cases the cardiac features are those of the ordinary intense febrile state—a mitral or a basic systolic murmur, not of great intensity and presenting no special characteristics. And lastly, with the most extensive valvulitis there may be neither symptoms nor physical signs pointing to the heart. (2) *Typhoid group:* Absence of detectable local focus of infection, irregular fever, delirium, dry tongue, occasional chills, perhaps diarrhœa, suggest the diagnosis of typhoid fever. Many of the severer forms of pneumococcic and gonococcic endocarditis are of this type. Embolic features are not so common, but there may be the same difficulty in determining whether the heart is really involved or not. It is in this group of cases particularly that the blood cultures are

of the greatest value, and the evidences obtained from lumbar puncture. But even the most skilful diagnosticians may be in doubt, and it may not be possible to say anything more than that a condition of septicemia is present. The illness lasts for from three weeks to three months, and the diagnosis may be made clear at any time by an embolic accident. Sometimes the whole picture is that of a meningitis. Even when no exudation is present, the headache, the progressive stupor, the cutaneous hyperesthesia, and the rigidity of the neck may strongly suggest it. It is to be remembered that in the pneumococcic form, and in others, too, meningitis is by no means a rare complication, and in several instances in which this complication occurred early it led to an erroneous diagnosis. Practically these two types, the pyemic and the typhoid, correspond to the two divisions of the suppurative and non-suppurative lesions.

A very interesting group of cases, the only one in which the diagnosis is easily recognized, is that to which Bramwell gave the name of (3) *cardiac group,* but which may be well called the *recurrent form.* In this

FIG. 4



Temperature curve in a severe attack of endocarditis.

the patient with chronic valve disease, mitral or aortic, begins to have irregular fever and an evening exacerbation of two or three degrees, an increase, perhaps, in his cardiac symptoms, and then embolic phenomena occur. The spleen enlarges and is tender, or there is pain in the back with bloody urine, or a sudden hemiplegia or a peripheral embolism may occur with gangrene. Such cases are very common, and while in some the process is acute, in others the symptoms may last for weeks or even months. These are the cases, too, in which after the severest symptoms recovery may take place. The chart given here shows the temperature record of such an attack in a man with mitral stenosis, who was under the writer's care on and off for many years and who had several attacks of severe endocarditis, from which he recovered.

This form, in which the patient has successive attacks, in the intervals of which he is afebrile and fairly well, is common enough as an incident in old cardiac lesions.

An *afebrile form* has been described, and we must recognize that a chronic septicemia may be present associated with endocarditis in which there is little or no fever. Even the very severe type with marked toxemia may be afebrile. Such a case has been reported by O'Donovan, of Baltimore, and lately a most distinguished London physician, himself a keen student of heart diseases, succumbed to an endocarditis lasting several months, practically afebrile, and without special cardiac symptoms.

Chronic Septic Endocarditis.—In reviewing the literature for the Gulstonian lectures on Endocarditis (1885), the writer was impressed by the protracted histories given by such keen observers as Wilks and Bristow. The chills, often recurring with great regularity, had suggested in these cases the existence of malaria. Bristow's case lasted for more than five months. Since then the writer has had a series of remarkable cases of what may be called the chronic septic endocarditis, in which the condition has persisted from periods ranging from four months to a year. Two of these were reported in the *Practitioner*, 1903. The main features are: (*a*) The presence of an old *valvular lesion*, aortic or mitral. An important point is the absence of any special change in the condition of the heart. In one patient, who had been under personal observation for a mitral insufficiency for fifteen years, at the end of a period of five months of daily fever (and nothing else) the condition of the heart was very much such as it had been years before, and yet the autopsy showed most extensive vegetative endocarditis. (*b*) *Fever*, which may be and often is the only symptom, with a daily rise of from 2 to 3 degrees. The chart shows an up-and-down septic temperature. Occasionally there are *chills*, but there may be fever of even a year's duration without any rigors. (*c*) *Emboli* are rare, but toward the close there may be high fever, petechiæ, and profuse sweats. Painful subcutaneous *nodules* of a peculiar form may be present, not exactly like the fibroid nodules of rheumatic fever, but rather resembling minute emboli of the skin. The spots are painful, reddish, slightly raised, and disappear in a day or two. (*d*) Anatomically the valves are found laden with vegetations, and the chordæ tendineæ are encrusted and often eroded. Infarcts are found in the spleen and kidney, but suppuration is not present. Pneumococci, streptococci, and staphylococci have been found in the vegetations. The cases appear to be more common in private than in hospital practice. The infection may persist for from three to four months to a year. In one of the cases reported, and of which the writer has a complete temperature chart, the fever lasted within two days of a year. In another the patient had a daily rise of temperature from the first week in December to September 16, nearly ten months.

Diagnosis.—There are two great groups of cases in the severer types. In the one endocarditis is only an incident in a general disease, and there may be no question of diagnosis, as nothing whatever in symptoms or physical signs may suggest endocarditis. It is surprising, indeed, in how many cases, particularly in pneumonia and in streptococcus septi-

cemia, the cardiac state is latent. The important points in the diagnosis are: the existence of a septic focus and a septic state, as indicated by the temperature, the blood cultures, etc.; the presence of petechiæ, embolic features, and small quantities of blood in the urine, and the symptoms and physical signs pointing to a valvular lesion. Where the septic element dominates, the endocarditis is usually overlooked. When the cardiovascular features are well marked the diagnosis is usually made.

In the second great group, in which the vegetations form the focus of a chronic septicemia, the diagnosis is by no means easy. The patients are the subjects of an old although often overlooked and well-compensated valve lesion. The fever begins insidiously, and for weeks the case may be treated as one of typhoid fever or the beginning of tuberculosis. Formerly malaria was suspected, but nowadays that is easy to exclude. Week after week, month after month, the daily rise of temperature may be the only feature, and, indeed, the patient may feel fairly well and be up and about for many weeks. The heart may present little or no change. An old apex systolic murmur indicating a mitral insufficiency may remain much the same. There may be very little enlargement of the heart. In the instance of aortic insufficiency the physical signs, as a rule, are more striking, the enlargement of the heart greater, and altogether the cardiac side of the case is more in evidence. So little change may there be in the state of the heart that on some occasions the writer had difficulty in persuading the attendant physicians of the serious nature of the cases until embolic features occurred.

Prophylaxis.—Much could be done to lessen the number of cases of rheumatic fever, of chorea, and of endocarditis if we attacked more vigorously and more systematically the enlarged tonsils of children. Here is the point toward which our efforts should be directed. A child subject to recurring attacks of tonsillitis, or with marked adenoids, should have the tonsils or adenoids thoroughly removed. Other measures of local treatment simply trifle with what is always a very dangerous condition. Physicians should be on the alert at the first indication of arthritis in the child to insist on absolute rest and to push the salicylates actively.

Treatment.—At the outset it may be questioned whether in endocarditis any measures are at our disposal worthy of the name of treatment. He must, indeed, have keen optimism who believes that we have any drug capable of influencing the state of the vegetations. In a case of simple endocarditis, particularly in rheumatic fever, these are the essentials in treatment: *Protracted rest* which favors the restitution of the valve. Probably the very slight warty growths may disappear without leaving any valvular thickening, but when there is infiltration of the tissue of the valve itself, sclerosis is an inevitable sequence. It seems absurd to talk about rest to structures which seventy or more times in the minute have to bear the full pressure of a ventricular systole, but it is relative rest if we diminish by one-third at least the amount of stress and strain which the mitral segments have to bear. They may be done by keeping the child at rest in bed. To be of any service it should be over a period of at least three months from the date of the fever.

Iodide of potassium may be given in moderate doses, in recognition of its control over vascular metabolism, a point which has been well brought out in experiments upon the experimental arteriosclerosis. Caton, of Liverpool, strongly recommends the application of small blisters over the heart. The writer has used these persistently in many cases, but is not able to say that any satisfactory results were evident. When there is distress about the heart, or palpitation, and particularly if pericarditis is present, an ice-bag may be used. When we can cultivate the organism of rheumatic fever and prepare vaccines, there may be some hope of mitigating and lessening the ravages of one of the most serious diseases of childhood.

The severer types of endocarditis are entirely beyond our control. The treatment is that of septicemia. In all cases an attempt should be made to determine exactly the infecting organism by culture. An autogenous vaccine has been used with success in a very few cases of severe endocarditis. The ordinary antistreptococcic serum which the writer has used in many cases has not proved successful in a single instance. There are instances, however, reported in which it has been successful. For gonorrhœal endocarditis an antigonococcic serum has proved beneficial in one recorded case.

And yet the condition is not always hopeless. As is well known, cases of severe sepsis, more particularly puerperal, may recover, and there are a good many instances in which, with all the features of very severe endocarditis, recovery has followed. J. B. Herrick has collected a series of such cases,[1] and he has given anatomical evidence of the healing of serious ulcerative lesion of the valve. Recovery may follow in the gonorrhœal and in the pneumococcic forms, although this favorable termination is rare.

[1] *Transactions of the Association of American Physicians*, vol. xvii.

CHAPTER VI.

HYPERTROPHY OF THE HEART.

By ALEXANDER G. GIBSON, M.D., F.R.C.P.

GENERAL CONSIDERATIONS.

Introductory.—Hypertrophy, a property possessed by most organs of increasing in bulk, and allied in the lower forms of life to the function of reproducing lost parts, is in the higher forms restricted to the production of a greater capacity for total work in particular organs. Under the general term is included hyperplasia, an increase in the number of normal cells, and true hypertrophy, which is an increase in the size of the cells themselves. In the following pages the term will be restricted to its more general meaning, for we are not yet able to specify to what extent the two processes participate in hypertrophy of the heart muscle.

Taking the single cell, we do not know how this process of hypertrophy is effected, and, indeed, a purely theoretical question such as this need not concern us. From the stand-point of the organ and of the organism, however, its conditions are better known, as definite anatomical features accompany equally definite circumstances, and from a study of such it is possible to form some notion of the stimuli by which it is called forth. Let us therefore attempt to answer the question, *What is the immediate stimulus to hypertrophy?*

From the fact that hypertrophy of an organ is invariably accompanied by an increase in its activity and, conversely, that any increase in activity if persisted in over a moderate time is followed by hypertrophy, it is probably true that the two processes are bound up with one another; it might even be said that hypertrophy is the anatomical expression of the increased activity. Just as the contraction of a muscle becomes the indirect expression of the activity of a nerve, so it is legitimate to infer that an increase in activity will be followed by hypertrophy; hence, if the conditions of increased activity of heart muscle are inquired into, stimuli will be found which give rise to hypertrophy. Heart muscle can be stimulated directly or indirectly by means of nerves, and the direct stimuli are mechanical, chemical, thermal, and electrical; the mechanical, chemical, and nervous stimuli are those that concern us here.

Mechanical.—Such stimuli may be of various kinds, but that which concerns us here is mechanical stretching or an increased resistance to contraction.

In skeletal muscle it is well known that stretching, especially sudden stretching, can stimulate sufficiently to cause a contraction. This is the explanation of the knee-jerk; it is a direct stimulation of the muscle fibres of the vastus internus by a sudden tension of its tendon, the reaction time being too short to allow of a reflex taking place. The presence of

an increased amount of urine in the bladder is associated with an increase in the rhythmical contractions of that organ. In the snail's heart contractions stop if the chambers are emptied by bleeding and begin again if pressure be again put into the system. Von Frey[1] has shown experimentally that an increase of resistance acts as a stimulus to the frog's heart and the amount of distension regulates the force expended in the beat. The time relations are too quick to allow of its being due to a reflex regulating mechanism, for the increase in force with an increase in distension often appears in the systole immediately following. Moreover, the mechanism is still present after the severance of all nerves. Of the relation of muscular volume to resistance, the conditions of the fetal heart are instructive and conclusive; Gibson and Gillespie[2] have shown that before birth the walls of the ventricles of the heart are of equal thickness; after birth, when the two cavities are entirely cut off from one another directly, the right ventricle increases in thickness at a much slower rate than the left. In fetal life the pressure in the two ventricles is approximately equal from the patency of the ductus arteriosus; after birth, when the umbilical artery is closed, the pressure in the right auricle immediately falls, the valve of Vieussens closes, and the ventricle requires no more, if as much, force to propel the blood to the left auricle through the lungs.

The increase of activity as a result of mechanical stretching is probably entirely apart from any nervous action, for Rieder[3] has shown that an increase in the work of the beat can be obtained even when all nerves are cut.

Chemical.—That a chemical substance circulating in the blood can increase the activity of muscle and cause it to increase in volume is probably true, but proof of it is not yet forthcoming. Of the substances to be thought of in this connection are veratrin, digitalis, adrenalin, and the cardiac tonics. A chemical element, again, may be present in renal disease or Graves' disease where heart changes occur, but the hypotheses of a chemical stimulus to heart activity in these diseases is as yet unproved; very significant is the recently established fact that renal disease with hypertrophy is always associated with hypertrophy of the suprarenal glands and sometimes with abnormality of the pituitary body. It has been found[4] that repeated injections of adrenalin will produce hypertrophy entirely apart from atheromatous changes; absinthe produces a similar condition.

Nervous.—Muscular tissue can be stimulated to increased activity by nervous action. In heart muscle there is little direct proof of hypertrophy following increased stimuli, because if we take the myogenic hypothesis as correct, the nerves of the heart have only a secondary effect in altering the muscle action. But considering skeletal muscle, ample proof is not wanting. If a nerve to a skeletal muscle be cut the

[1] *Deutsch. Arch. f. klin. Med.*, 1890, vol. xlvi, p. 398.
[2] *Edinburgh Medical Journal*, 1892, vol. xxxviii, p. 429.
[3] *Deutsch. Arch. f. klin. Med.*, 1895; quoted by Thorel in *Lubarsch und Ostertag's Ergebnisse der Pathologie*, 1904, p. 797.
[4] Grober, *Deutsch. med. Woch.*, 1907, vol. xxxiii, p. 744.

latter degenerates, while if the nerves be more frequently stimulated, as, for instance, by electricity or by use, the muscle hypertrophies. In regard to the relation of nervous action to cardiac hypertrophy only indirect evidence is available. Hering has recently found that if the heart is in standstill, stimulation of the sympathetic nerve supply will cause the heart to beat; it has long been known that stimulation of the sympathetic nerves to the heart will produce a faster rate and a more powerful beat than in the normal condition. A few conditions met with clinically point to this cause as the origin of conditions of hypertrophy. In neuritic lesions of the brachial plexus, especially the left side, it is not unusual to find evidence of some hypertrophy of the heart (Potain). The slight hypertrophy that is met with in the neurotic persons is probably of this nature. Moreover, such may be the cause of the hypertrophy that is found as a result of excessive sexual indulgence and that sometimes associated with growth.

Nutrition and Hypertrophy.—The relation between hypertrophy and hyperemia is very close, and in heart muscle probably plays a very essential part in the ultimate establishment of that process. Instances in general pathology of hyperemia causing hypertrophy are sufficiently numerous, as, for instance, after cutting the cervical sympathetic nerve on one side of the neck of a rabbit a more vigorous growth of hair on that side results. In skeletal muscles the sequence of events is probably this: increased activity of muscle from stimuli arising from motor nerves, increased contraction of muscle, afferent impulses then travel up and reflexly cause dilatation of the muscular arterioles, and the increased nourishment thus supplied causes a direct increase in the size and probably the number of the muscle fibres. By analogy the same process may occur in the heart; the increased contraction may be brought about by any one of the conditions just enumerated; this then causes reflexly a hyperemia of the muscle and consequently an hypertrophy of the muscle fibres. Or another possibility is that the increase in aortic pressure produced by an increase in heart activity forces more blood into the coronary arteries. Albrecht,[1] from an examination of a number of hearts in which hypertrophy was present, strongly advocates the view that hypertrophy is a true inflammatory process or a proliferating myocarditis. He finds changes of the nature of hypertrophy to occur in the neighborhood of undoubted foci of inflammation. But it may be doubted whether Albrecht's view expresses more than a portion of the truth. If it be true that hyperemia in heart muscle produces hypertrophy, then hyperemia, whether general, as from reflex nervous processes, or local, as from a small inflammatory focus, will cause the muscle to react in the same manner in either case. Moreover, other authors[2] have not been able to confirm Albrecht's proposition that in hearts, *e. g.*, from cases of hypertrophy from renal disease, there are foci of inflammation, unless produced by an accompanying sclerosis of the coronary vessels. Krehl is of the opinion that increased nutriment of itself does not lead to hypertrophy of the heart, but only when it is associated with an increase of activity,

[1] *Der Herzmuskel*, Berlin, 1903.
[2] See Aschoff and Tawara, *Grundlagen der Herzschwäche*, Jena, 1906.

for an increased pressure in the coronary arteries does not necessarily lead to hypertrophy of the right ventricle (*e. g.*, in renal disease); but it has lately been determined that the area of dogs' hearts as shown by the orthodiagraph increases with an increase of diet.

That hypertrophy is not dependent on adequate general nutrition has been proved by Tangl, who, after producing an artificial insufficiency of the aortic valves in starving dogs, still found hypertrophy to occur.

HYPERTROPHY AS OCCURRING IN A NORMAL HEART

The Relation between Muscular Work and Hypertrophy.—A number of conditions of life, chiefly those associated with muscular exertion, lead ultimately to hypertrophy of the heart. As Clifford Allbutt pointed out in 1870, many laborious occupations lead to marked hypertrophy and cardiac failure. When muscular work interferes with function it would be classed under cardiac insufficiency, which will be discussed later. We are, however, justified in thinking, from the results of certain observations which will be mentioned, unfortunately by no means complete as proof, that increased muscular work, when carried out under conditions which are within the physiological limits for the particular person, leads to a certain amount of cardiac hypertrophy—an hypertrophy which is associated with the necessity for a widening of the amplitude of cardiac response, for the setting free of many times the energy that is given forth at rest. This property of the heart to be able to accomplish more than it has done at rest is called reserve power. The normal heart, when the body is at rest, does an amount of work which is determined by certain internal needs of the body, by far the most important of which is an adequate supply of blood to the skin to balance the heat lost by cooling.

In this relation it is absurd to suppose that an hypertrophied heart, that only possesses a greater breadth of reserve power than the non-hypertrophied, does more work at rest than corresponds to the needs of the body. The heart hypertrophied as the result of work differs from the normal heart in that it possesses a much greater amplitude of reserve power, *i. e.*, the demand which can be put on the hypertrophied heart because of its breadth of reserve power is many times greater than in ordinary hearts. But it is doubtful if all increase in the reserve power means an increase in heart muscle; certain experiments of the writer, as yet unpublished, show that an increase in hemoglobin and possibly some lessening of blood volume occur long before any hypertrophy is evident; in fact, clinically, the hearts of athletes engaged in ordinary contests, such as football and rowing, are not enlarged.

Külbs[1] finds an increase in the weight of the heart in proportion to the degree of work performed. He took two pairs of dogs, the dogs in each pair being as nearly similar as possible in weight, build, and age. He then subjected them to exactly similar conditions, except that one was made to do work on an endless stage. In both experiments there

[1] *Archiv. f. experim. Path. u. Pharm.*, 1906, vol. lv, p. 288.

was a marked increase in the weight of the heart in the animal that had done work. Thus the relation of heart muscle to skeletal muscle in the controls was respectively 1 to 53.9 and 1 to 59, and in the animals subjected to work 1 to 37.4 and 1 to 37.7 respectively—a proportion which is exactly that of the relation of the heart muscle to skeletal muscle in the deer. The increase affected the right as well as the left side. But the increase of heart muscle was much greater in proportion than that of the skeletal muscle, Thus in one pair the increase in heart weight was 53 gm. from 99 gm. (the weight of the control animal's heart) and the increase in skeletal musculature was 354 gm. from 5342 gm. (the weight of the control animal's musculature). If the skeletal musculature had increased in the same proportion as that of the heart it should have been 8201 instead of 5696 gm. in the working animal of the first pair and 10,313 instead of 6498 in that of the second pair. There was a

FIG. 5

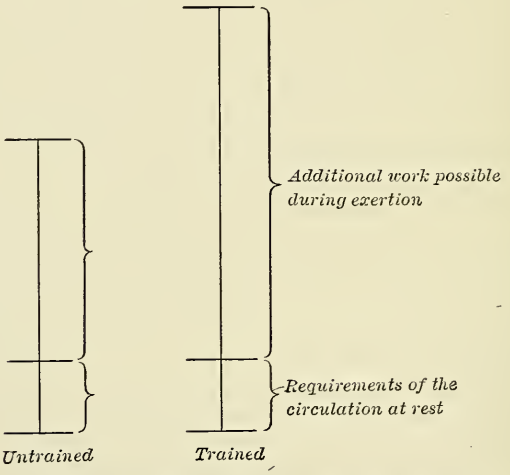


Diagram to show the difference between the heart of an untrained person and a trained athlete.

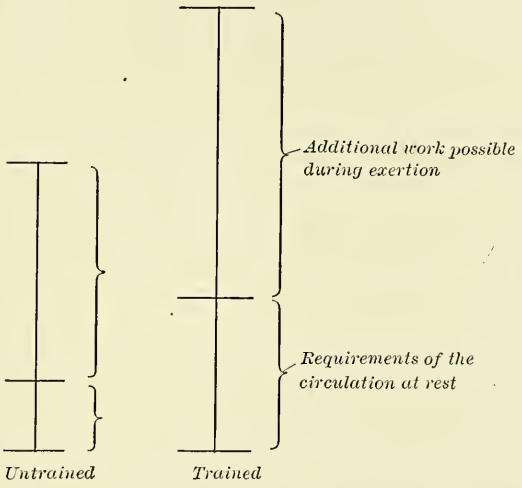
marked increase in the weight of the liver, spleen, kidneys, lungs, and pancreas, especially the first; it is therefore possible that the increase in work of these organs from metabolic reasons requires a further increase in the heart weight.

Grober[1] has weighed the total heart and its parts of rabbits kept in confinement, wild rabbits, and hares, and finds a much heavier heart in the wild rabbits than in the tame and in the hares than in the wild rabbits. This order corresponds with the degree of their muscular activity. The enlargement affects the right side of the heart more than the left; thus, in one instance quoted the left ventricle of the tame rabbit weighed 0.989 gm. while that of the hare weighed 2.840 gm., about thrice the amount; and the right ventricle of the tame rabbit 0.462 gm., of the hare 1.860 gm., more than four times the amount.

[1] *Deut. Arch. f. klin. Med.*, 1907, vol. xci, p. 502.

When the strain of muscular work is greater than it is possible for the person to withstand, owing to the continued high pressure in the cavities of the heart, there is a failure to expel the whole of the blood brought to the ventricle; the consequence is a *dilatation* of one or more of the cavities of the heart for the time and an interference with the proper action of the cardiac muscle. In such a person at rest, in order to expel the necessary amount of blood into the aorta, the heart at each systole would have to exert, by reason of the dilatation of its cavity, a greater pressure per unit area of its internal surface than a heart whose cavity was not so dilated. The amount of work expended in such a heart per unit of time would be greater than in the normal heart even at rest.

FIG. 6



Digram to show the difference between the heart of an untrained person and an athlete whose heart is beginning to enlarge as the result of overstrain.

However difficult such distinctions may be to recognize clinically, it is highly necessary to do so theoretically; for while the athlete whose heart requires no increase of work to carry on the bodily functions at rest is normal, the one whose heart is working more than it should do at rest is running a serious risk of heart failure in the near or remote future.

In this section it is desirable to treat only of those conditions in which there is no reason to suspect an increase of heart requirements during rest. The conditions under which normal hypertrophy occurs are:

1. The hypertrophy of growth.
2. From the use of ski.
3. In consequence of cycling.
4. In mountain dwellers.

1. **The Hypertrophy of Growth.**—It has been asserted, especially by French writers, that children and young people about the age of puberty frequently show both objective and subjective signs pointing to an

hypertrophy of the heart. Judging from the published accounts of the cases, the condition is one with occasionally some enlargement of the heart, especially to the right, with increased force of the beat, as felt in the chest. We require, therefore, further evidence on the point whether the heart at rest is acting with more power. Seeing, however, that it is a phenomenon seen in children with no suspicion of disease, it is well to insert it at this stage, and not leave it to be included among the abnormal causes of hypertrophy.

2. **Hypertrophy from the Use of Ski.**—The use of *ski* for the purpose of locomotion is attended with but ordinary exertion on even ground, but in rough or hilly regions the efforts required are maximal. Henschen was able to determine in Laplanders the presence of hypertrophy of the heart; if not of the whole heart, yet certainly of the left ventricle.

3. **Hypertrophy in Consequence of Cycling.**—Schieffer,[1] investigating by means of *x*-rays and percussion the size of the heart in young men of the age of military service, finds that habitual use of the cycle causes a definite increase in the size of the heart area. He finds that even hard occasional cycling does not produce any result which can be determined by his method, but that if a cycle is used continuously for three years such evidence is always forthcoming, and if it is continued for a longer period the hypertrophy increases. Both the transverse and the longitudinal diameters of the *x*-ray picture are increased and consequently the total area. In 13 out of 35 men who had used cycles for three to fifteen years the superficies of the heart exceeded by 25.9 sq. cm. the normal (even up to 35 sq. cm. in some). The normal areas are obtained for the corresponding heights and weights from Dietlen's[2] figures. Whether the size of the heart's area is taken in proportion to the weight or height, it still shows an increased proportion from 5 to 29 per cent.

It is only right to say that Schieffer himself believes that there is in all these hearts examined an abnormal dilatation, and that it is an abnormal condition. He supposes, although he has no direct proof, that such persons are more in danger of heart failure than others. From one point of view, however, being otherwise normal men in a healthy condition, they can stand as much strain as other young adults. But from clinical examination of the apex beat, percussion, auscultation, etc., a certain number are evidently abnormal. Thus, 4 out of 71 individuals had an apex beat outside the nipple line, 11 had it in the nipple line, 30 almost in the nipple line, while 20 had it within. In 14 there was a systolic murmur at the apex and 44 had an accentuated pulmonary second sound. It may be doubted if all these are normal, but it is probably right to assume that a certain proportion had hearts which showed no signs of dilatation or insufficiency at rest.

4. **In Mountain Dwellers.**—The volume of the heart muscle in animals bears a definite proportion to the amount of work which the animal's habits of life necessitate. The same has been shown for human beings living in mountainous districts as compared with those living in the plains. In the first place it is well known that heart failure is much

[1] *Deutsch. Arch. f. klin Med.*, 1907, vol. lxxxix, p. 604.
[2] *Ibid.*, 1906, vol. lxxxviii, p. 55.

more common in very mountainous districts than in flat countries. Mosso (*Der Mensch auf den Hochalpen*) mentions this fact, and that the majority of old persons die of heart failure. The "Tübingen heart" is a classical example of heart failure the result of arduous labor in a hilly district. These facts suggest that in normal persons the heart must be heavier than in those who do no arduous daily work.

Kalmansohn[1] has investigated the hearts from 379 patients not dying of heart disease or associated with any obvious cause of hypertrophy. He finds that the average weight of the heart for corresponding age periods of twenty years is greater in Zurich than that obtained by Müller in Jena and Peacock in London. It affects women as well as men, but the former not so markedly—and the differences become less marked, especially in women over the age of forty years. In most of the patients no abnormality had been detected in the heart during life. We shall probably be right in assuming, as does Kalmansohn, that in them a larger amount of bodily exertion necessitated an increase of muscular tissue in the heart.

Anatomy and Histology.—We have yet to learn from actual data whether in these cases the cavity of the heart is enlarged or not, whether such hearts are to be looked upon as concentrically or excentrically hypertrophied. Moritz conceives it impossible to have an increase in the size of the fibres of the heart wall without a corresponding increase in the internal surface; but the very fact of there being a concentric hypertrophy in the newborn child and in children up to the tenth year[2] suggests that an increase in growth is not necessarily associated with an increase in the size of the heart cavities. On the other hand, if we suppose that the tonicity of heart muscle is variable, it is probably true to say that when heart tonicity is great the muscular walls are well knit together and the cavities smaller, in the same manner as, for instance, in rigor, than when tonicity is at a lower level. Further work is required to give more insight into these conditions, and all we can suppose at present is that in the hypertrophy of work new relations are set up in the heart, which, with an increase in the bulk of its muscle, put no additional burden on the mechanism when the person is at rest.

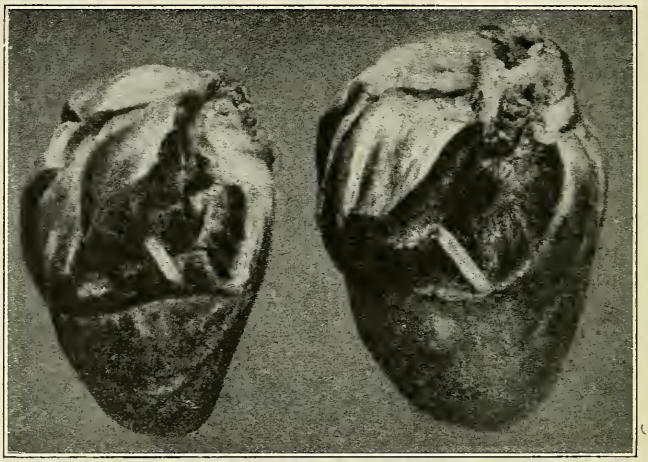
So little is known of the conditions that exist in man that what knowledge is available is derived from the study of the hearts of animals under experimental conditions. Külbs, for instance, in the dogs which have been subjected to work compared with dogs not so treated, finds the heart increased in size as a whole and showing an increased thickness of the walls of the left ventricle, right ventricle, and ventricular septum (Fig. 7). Grober finds that the right ventricle is increased more than the left, and mentions that in the animals of active habit the parts not weighed (auricles) appear to be increased in proportion to the others. Owing to the technical difficulties, nothing certain is known of the size of the cavities of the heart.

Histologically such hearts are sharply demarcated from hearts hypertrophied as the result of a valvular lesion. The fibres are not increased

[1] *Diss. zur Herzgewicht*, Zurich, 1897.
[2] Parrot, quoted by Thorel, *Ergebnisse der Pathologie*, 1903, p. 759.

in size, nor do they show an increase in the amount of sarcoplasm. An increase of interstitial tissue is not present.

Fig. 7



Heart of normal dog, 99 gm. Heart of dog subjected to work, 152 gm.

Diagnosis.—Ex hypothesi we have defined this type of hypertrophy as one which is developed only for special times during the period of

Fig. 8

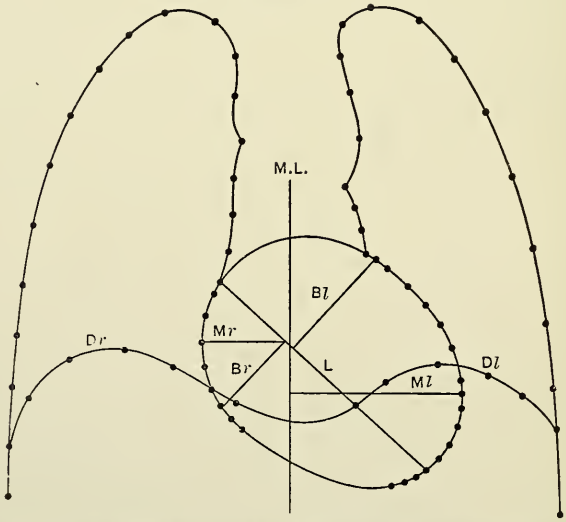


Diagram to show the method of measuring an orthodiagram of the heart: *L*, long diameter; *Br*, *Bl*, breadth to right and left sides respectively; *Mr*, *Ml*, breadth to right and left respectively, taken in the horizontal direction; *ML*, middle line; *Dr*, *Dl* = right and left sides of the diaphgram respectively. The dotted line shows the lines which are marked in at the time of taking the orthodiagram. (After Dietlen.)

exertion. Symptoms are therefore out of the question except during the period of exertion at the limits of cardiac endurance. Further,

many of the usual signs of hypertrophy, increased power of the apex beat and accentuated second sound at the base, are probably not evidence of hypertrophy so much as of the overaction which is necessary even during rest to combat the effects of interference against which the hypertrophy is the normal reaction. We would arrive, therefore, at the opinion which is corroborated by physicians of the widest experience, that a heart which at rest gives signs such as a heaving or diffuse apex beat, with a strong pulse and accentuated second sound, is one which is less efficient than one in which the apex is localized and not forcible, with no marked increase in pulse volume and with no accentuated second sound. In other words, an hypertrophied heart which is doing more work at rest than a normal heart is one which cannot run the same risk as one which does not show such signs.

Da Costa mentioned the difficulty of accurate delimitation of the size of the heart, and asserts, what is highly probable, that hearts of very different size are put down as normal. With the use of the *x*-rays it is now possible to estimate with considerable accuracy the size of the outline of the heart as shown on the screen, and the results obtained amply justify Da Costa's supposition. Dietlen[1] has recently recorded his observations on the size of the normal heart by means of the orthodiagram, at the same time comparing with this the results of percussion. The examinations were made on 187 men and 74 women, all free from cardiac or severe skeletal disease. He finds that the size of the heart varies somewhat with the height, but a much more constant relation exists between the weight and the size of the heart area; that the mammillary line bears no fixed relation to the height or weight, varying in men from 8 to 13 cm. from the midline; therefore, information as regards the apex beat made with reference to the nipple line is not of much value. The size of the heart increases with age and sinks with the diaphragm lower in the chest. The apex beat is generally felt in the intercostal space above that in which by the *x*-rays the apex is thought to be.

Percussion of the heart in the hands of men who have tested their results by means of *x*-rays appears to give highly accurate results except in one or two conditions, such as emphysema of the lungs. No special form of percussion seems to give more accurate results than another. Goldscheider[2] has recently advocated the original method of Auenbrugger, of very light orthopercussion. Ebstein recommended tactile percussion and Moritz the ordinary method with two fingers, using heavy percussion for determining the right border and medium or light percussion for the left, which is less easy to define.

HYPERTROPHY AS A DEFENCE AGAINST A PATHOLOGICAL CONDITION.

The hypertrophy we have previously dealt with has been such as only served to increase the total activity of the heart at certain times;

[1] *Deutsch. Arch. f. klin. Med.*, 1906-07, vol. lxxxviii, pp. 55 and 286; see also Simons (p. 246) and Moritz (p. 277).

[2] *Deutsch. med. Woch.*, 1907, vol. xxxiii, p. 1121.

we have now to examine the conditions under which for the proper upkeep of the circulation a constant increase in heart work is required. Broadly speaking, the one cause of such necessity is *an increase in the residual blood in the heart chambers after systole;* such an extra amount of blood, together with that which flows in during the diastole, requires a larger cavity at the beginning of systole than formerly. In order to effect the required transference of blood into the next chamber or tube the same pressure must be communicated to the liquid as before, this being given to the liquid by the contraction of the walls of the cavity. But in order for the amount of blood to be at the same pressure as formerly the same pressure per unit area of the internal surface of the cavity must be given as before; hence, if the internal surface is greater the total required is greater and the heart must beat more strongly. But an increased activity when continued leads to hypertrophy. Such an example would apply to the conditions occurring after a lesion to a valve or a dilatation of the heart the result of a strain. If the lesion causes a permanent increase in the residual or diastolic blood in the heart, then the cavity of the heart is permanently enlarged and the hypertrophy which develops is probably also permanent. The dilatation would then be spoken of as *compensatory,* and although when compensatory dilatation becomes great, it may merge gradually into the dilatation associated with and accompanying some forms of chronic cardiac insufficiency, in the forms with which we are here dealing, in which the circulation is compensated for rest, it must be clearly distinguished from heart failure.

FIG. 9

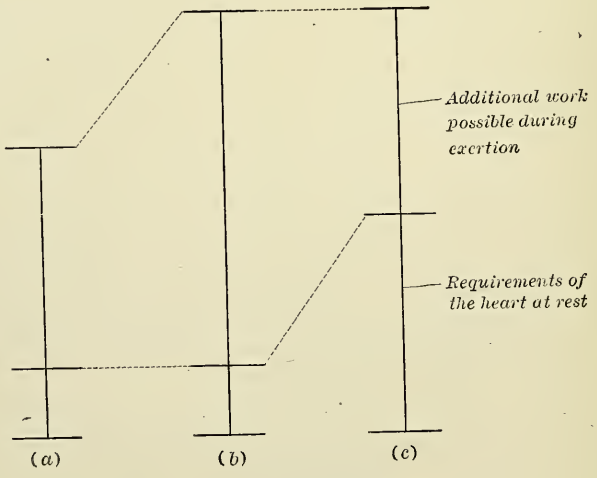


Diagram to represent the three stages of hypertrophy: *a* is a normal heart; *b* is that of an athlete in training; *c* is a heart which has undergone compensatory dilatation and consequent hypertrophy.

The accompanying diagram represents the conditions of the heart in three stages: *a* is a normal heart; *b* a heart with an increase of reserve power, such as a heart hypertrophied as the result of muscular exertion,

and *c* is a heart which has undergone compensatory dilatation and consequent hypertrophy.

Etiology.—1. **From an Interference with the Heart as a Contracting Organ.**—(*a*) *Overexertion* has long been known as a cause of hypertrophy beyond the limits of the normal heart, and is now fully recognized as a very important cause of non-valvular disease of the heart. We have no reason to suppose that in the majority of cases any other factor is concerned than the strain on the heart due to the exertion, although in some cases other factors, such as a previous infection or alcohol play, a part. It matters not to what class a person belongs, any prolonged or very arduous exertion will sooner or later lead over and above an hypertrophy of work to an hypertrophy which is also associated with compensatory dilatation. We lack sure evidence of the extent to which hypertrophy coming on in foundrymen, hammermen, and others in early middle life is not to some extent due to alcohol or syphilis. The same suspicion can hardly be entertained with regard to the majority of men engaged in college athletic sports, many of whom, from their school-days, have led very careful lives. Even in these, however, we cannot eliminate the effect of a previous infection, an attack of diphtheria or pneumonia, which would detract from the total accommodation power of the heart muscle. Yet, further, certain families are notably long-lived, probably, in chief part, because of particularly good cardiac muscle. Such hereditary endowments, upon whatever they depend, can hardly fail to influence the degree to which muscular work can be pushed without causing hypertrophy. As an example of marked hypertrophy from overexertion the following case may be cited: An undergraduate, aged twenty years, while rowing in the summer "eights," "crocked" and was advised not to row any more; he was examined by a London consultant and pronounced to have "two murmurs," according to the patient's account of himself. He was advised to take life easily and avoid any overexertion. About six months later he was seen while suffering from an attack of influenza of a mild gastro-intestinal type, and, being told of his heart condition, the writer examined his heart carefully and could find no sign of any cardiac disease as he lay in bed; his apex beat was well within the nipple line, the sounds were clear, and there was nothing to suggest any abnormality. Seven months later he complained of a feeling of giddiness and some palpitation, coming on at night after playing tennis. In the upright position his apex beat was in the sixth interspace, one-half inch outside the nipple line, fairly localized and forcible; there was pulsation in the fifth space and in the epigastrium. There was no dilatation of or marked pulsation in the veins of the neck. On auscultation there was a definite systolic murmur at the apex traceable a short distance toward the axilla. The second sound at the apex was reduplicated. At the base there was a well-marked systolic murmur not heard in the vessels of the neck or below the region of the valves. No history of any infection could be elicited, and he was a person of excellent habits of life.

From observation of patients and examination of reports, hypertrophy may affect chiefly the left or the right side, and there are intermediate

cases in which both sides are equally affected. Such differences are probably to be attributed to the position of the resistance which is placed in the circulation. If the obstruction is chiefly in the systemic system, caused by contraction of muscles, we would expect the left heart to hypertrophy; if the work required great and prolonged fixation of the walls of the thorax, the obstruction to lung circulation through increased pressure in the alveoli would most affect the right side of the heart.

The following case quoted by Da Costa is a good example of a left-sided hypertrophy following overexertion: The patient was a soldier who suffered from dyspeptic symptoms and constipation, and used tobacco to excess. In 1863 he had severe palpitation which unfitted him for active duty. The heart impulse was wider than normal and the first sound rather weak, but there were no signs of hypertrophy. The condition was regarded as one of irritable heart. In 1870 there was decided hypertrophy. The transverse cardiac dulness was increased, the impulse wide and forcible, and the apex beat lowered. The first sound was prolonged and murmurish. He had some shortness of breath and palpitation, with inability to undergo any great exertion. In another, not so marked, case at postmortem there was hypertrophy of both ventricles and dilatation, the greatest hypertrophy being of the left ventricle.

(*b*) *Hypertrophy as the Result of a Valvular Lesion.*—This is discussed in the articles dealing with the different valvular lesions.

(*c*) *Hypertrophy from an Obstruction to the Circulation in the Efferent Vessels from the Heart.*—The chamber which pumps blood toward the obstruction tends to be incompletely emptied owing to a diminished onflow in the arteries; the incomplete emptying produces additional stretching of the chamber walls, greater pressure in diastole, and subsequent hypertrophy. The conditions which fall in this section naturally group themselves into those which cause hypertrophy of the right and those which cause hypertrophy of the left side of the heart. Of the former we have emphysema, chronic bronchitis, dilatation of the bronchi, asthma, fibrosis of the lung, lesions of the left side of the heart, and sclerosis of the pulmonary artery. In these conditions a marked epigastric pulsation and an enlargement of the deep dulness well outside the normal limits are of frequent occurrence.

Lichtheim[1] has shown that if the sectional area of the pulmonary circulation be lessened to one-fourth of the normal, hypertrophy of the right ventricle of the heart follows. Hirsch has shown that the degree of hypertrophy in the right heart in emphysema is proportional to the extent of the change in the lungs. The left ventricle under such conditions is either of normal weight or slightly under normal. In pulmonary tuberculosis, even with great fibroid change, hypertrophy of the right ventricle is by no means constant, and when present bears no intimate relation with the degree of lung disease. Hirsch[2] has shown that the hearts of persons dying from pulmonary tuberculosis are smaller than normal; hence the two factors would tend to neutralize one another.

[1] *Die Störungen des Lungenkreislaufs*, Berlin, 1896.
[2] *Arch. f. klin Med.*, 1899, vol. lxiv, p. 596.

Several cases have been described[1] of right-sided hypertrophy of the heart as a result of sclerosis of the lung arteries. Leonard Rogers has described a number of cases probably syphilitic in origin among natives in India.[2] This is frequently present in anthracosis and in those dying in pauper asylums, and is wholly distinct from changes in the lung arteries the result of mitral disease.

With a lesion of the left side of the heart, *e. g.*, mitral regurgitation or mitral stenosis, the left auricle sooner or later is unable to accommodate the extra blood which it receives, the lung system becomes overfull, and this again reacts on the right side of the heart, causing the necessity for greater pressure in order to drive forward the necessary amount of blood; hence the hypertrophy of the right ventricle.

Hypertrophy of the Left Ventricle.—Arteriosclerosis of the systemic arteries has long been known to be associated with hypertrophied heart, but not in all cases does arteriosclerosis even of a marked grade lead to such changes. Affections of two portions of the arterial system are invariably associated with hypertrophy: one is arteriosclerosis of the aorta and the other is arteriosclerosis of the splanchnic vessels. In both these instances the hypertrophy must be looked upon as a direct consequence of the change in the vessels.

The aorta with which hypertrophy is associated is dilated. It has been recently shown by Bittorf[3] and by Strasburger[4] that the elasticity of the aorta in these cases is diminished, *i. e.*, the extensibility is increased; consequently, if a certain volume of blood is propelled into such a vessel it dilates more than the normal, less blood gets to the periphery, the blood pressure is lowered, and reflexly the heart is stimulated and finally becomes hypertrophied. When the aorta has become dilated there is less tendency for it to return to its normal size because of anatomical changes which have taken place in it (formation of fibrous tissue, etc.). Hence, one would now consider the hypertrophy as a compensatory condition to the aortic dilatation, and not *vice versa*. Probably to this cause must be attributed the hypertrophy of the senile heart.

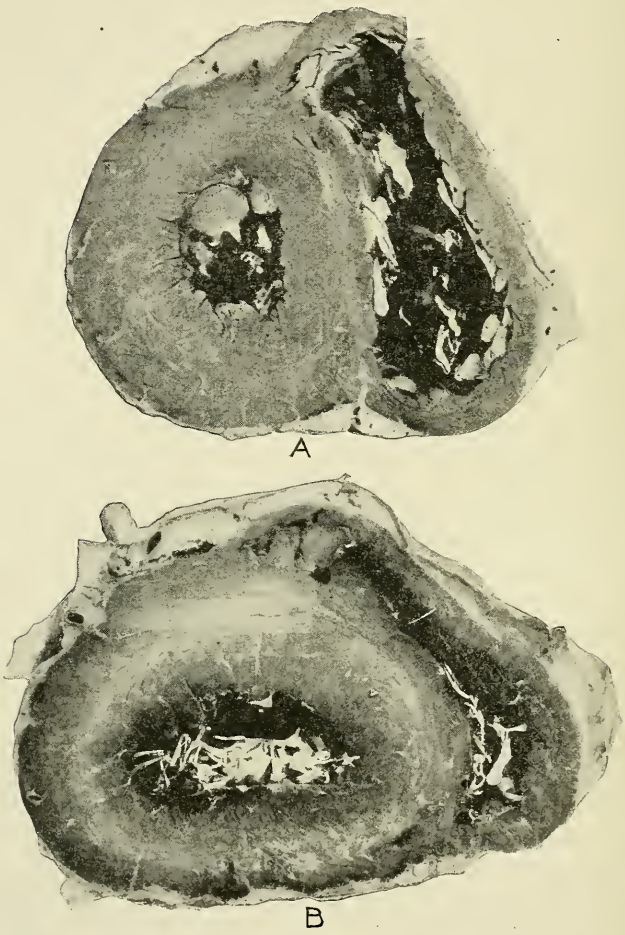
Hasenfeld,[5] in a study of 14 cases of hypertrophy from arteriosclerosis, found in all of them a sclerosis either of the aorta above the diaphragm or of the splanchnic vessels. Of these 14 cases 10 were purely arteriosclerotic in nature, while 2 were the result of kidney disease.

The hypertrophy of the left ventricle, which with such constancy accompanies renal disease of the chronic forms may in a large number of cases be due to a sclerosis of the splanchnic area, as suggested by Hasenfeld. Such, however, can hardly account for cases of hypertension in renal disease twenty-four hours after the onset and leading to hypertrophy. There is agreement that the hypertrophy of the heart is secondary to the renal disease and is most frequent and most marked in the chronic forms. There are no forms of heart special to particular forms

[1] Romberg, *Sclerose der Lungenarterie, Deutsch. Arch. f. klin. Med.*, vol. xlviii, p. 197.
[2] Leonard Rogers, *Quart. Jour. Med.*, Oxford, 1908–09, vol. ii, p. 1.
[3] *Münch. med. Woch.*, 1907, vol. xviii.
[4] *Cong. f. inn. Med.*, 1907. Abstract in *Münch. med. Woch.*, 1907, vol. liv, p. 1052.
[5] *Deutsch. Arch. f. klin. Med.*, 1897, vol. lix, p. 193.

of kidney affection. Sometimes the right ventricle as well as the left is hypertrophied; this is explained as being due to toxemia or by some as due to the coexisting chronic lung changes, by others as being due to the increased blood pressure in the coronary arteries, and hence the increased nutriment to both chambers.

Fig. 10



A is a section of a normal heart; *B* of a heart hypertrophied as the result of renal disease.

It is still not possible to decide which of the two rival hypotheses, the *mechanical* or the *chemical*, is the correct explanation of the production of hypertrophy. According to the first, known as Traube-Cohnheim's theory, the cutting off of a portion of a capillary system causes a rise in aortic blood pressure. Cushing, for instance, finds that an increase in the pressure in the cranial cavity, until the pial vessels become blanched, causes reflexly a stimulation of the heart until the pressure has risen sufficiently to make the vessels patent again. But against this,

excision of one kidney is not always followed by hypertrophy, and tying both renal arteries is not followed by an increase in aortic blood pressure.

The second or chemical hypothesis of Bright, Johnson, Rosenbach, Senator, etc., supposes a failure in the excretion and a stimulation of the heart by the unexcreted material in the blood, either directly or indirectly, by causing contraction of the small bloodvessels. But hypertrophy can occur without a demonstrable excess of urinary constituents in the blood, and the injection of large quantities of urine into animals does not produce any marked effect on the circulation. The viscosity of the blood is not altered to a degree sufficient to account for the hypertrophy.

(*d*) *Mechanical Obstruction to Respiration.*—Any obstruction to the expansion of the chest during respiration will give rise, if long continued, to hypertrophy of the heart; just as fixation of the chest in certain bodily exercises causes some degree of right heart embarrassment, so any obstruction to normal respiratory movement, by causing more force to be expended, gives rise to hypertrophy.

Pleuritic Adhesions.—An association between this and right-sided heart hypertrophy has been noted.[1] There is some other factor, however, causing the hypertrophy, for cases with few or localized adhesions very often give rise to considerable hypertrophy. In some, diaphragmatic adhesions, by which the movements of the diaphragm are impeded, give rise to considerable hypertrophy, yet the amount of hypertrophy from pleuritic adhesions is not in proportion to the extent of the diaphragmatic affection.

Deformities of the chest almost invariably give rise to some hypertrophy of the right heart. It is an hypertrophy of the whole ventricular wall, and not only the conus portion, as has been supposed. No satisfactory explanation has yet been given of the mechanism of this form of hypertrophy; it has probably to do with the interference with lung movements or the anatomical changes consequent upon it. Under this section also comes a right-sided hypertrophy, which has been described by Macnaughton[2] in choristers.

(*e*) *From an Interference with the Heart from Without.—Obliteration of the Pericardial Sac.*—Two forms of obliteration from pericarditis must be distinguished: First, the cases in which the two layers of the pericardium are adherent, and, second, when, in addition to the adhesion between the two layers, there is also an extension of the cicatricial tissue to the extrapericardial tissues, thus anchoring the heart to the neighboring structures. The second type only is associated with cardiac hypertrophy. The older view, that adhesions between the heart and other resistant structures, such as the sternum, opposed a number of hindrances to the proper contraction of the ventricle and consequent propulsion of blood, has in recent years been doubted. It has been shown, for instance, that the hypertrophy bears no relation to the degree of cicatricial fixation and that the synechiæ may be only slight and yet the hypertrophy may be great. It has been supposed in these cases that

[1] Bäumler, *Deutsch. Arch. f. klin. Med.*, 1877, vol. xix, p. 471.
[2] *Lancet*, 1905, vol. ii, p. 1136.

the hypertrophy is more probably due to other complications, such as lung changes, valvular changes or arteriosclerosis. It is impossible to say to what degree these objections are valid; certain it is that the contracting bands have some, if not the whole, effect, as witness the good results of setting free the heart from its fixation by surgical measures.

French writers describe a form of enlargement of the heart, probably of the nature of hypertrophy, which is found in patients with large abdominal tumors; the causation is not clear. It may be due to some mechanical embarrassment of the heart, a reflex irritation of the heart from the abdominal sympathetic, or a compression of the great vessels of the abdomen and a compensatory increase in aortic blood pressure, as in one explanation of the hypertrophy of renal disease.

(*f*) *Hypertrophy from Interference with Cardiac Muscle.*—The diseases of cardiac muscle are treated elsewhere and this aspect of hypertrophy therefore need not be considered very fully. The interferences with cardiac muscle giving rise to hypertrophy are degenerations and myocardial changes from coronary artery disease, parasites, and new growths. Of these myocarditis and coronary artery disease produce by far the greatest hypertrophy. On the other hand, degenerations, such as fatty degeneration, are seldom associated with hypertrophy, and in the published accounts of parasites and new growths of the heart hypertrophy was not as a rule evident postmortem; so that the power of most of these causes to produce hypertrophy, except those which are treated of elsewhere, is very small.

2. **Hypertrophy from Stimulation of Nerves.**—From what has been said on the immediate stimulus which causes hypertrophy, it follows that an excessive stimulation of the sympathetic nerves of the heart causing an increased rate and force of the beat will ultimately lead to hypertrophy. One of the most marked examples, as well as one of the most frequent, is that which accompanies Graves' disease. We are not in a position to say to what extent a direct chemical stimulation of the muscle fibres by thyroid secretion acts, but pending further knowledge we are justified in including it under this heading.

The hypertrophy which results from excessive sexual indulgence is probably of this nature. Finally, there are cases in which hypertrophy appears to be due to reflex irritation of the nervous centres of the cardio-acceleraton centre. Potain was the first to point out that reflex disturbances, such as dyspnœic attacks, which were the result of chronic dyspepsia or catarrh of the bile passages, produced hypertrophy with enlargement of the right heart. This form is fully discussed by Barré.[1] Potain also drew attention to the hypertrophy which follows lesions of the brachial plexus, neuralgias, neuritides, neurosis, and neuromata, a reflex irritation and increased activity.

3. **From an Abnormal Chemical Stimulus.**—*Alcohol.*—The effects of excessive beer drinking have been sufficiently emphasized by Bauer and Bollinger[2] in their researches on the conditions of the heart in Munich autopsies. While it may be doubted whether the conditions they found

[1] *Rev. de. méd.*, Paris, 1883, vol. iii, p. 1.
[2] *Festschrift f. Pettenkofer*, München, 1893.

were due to the excess of fluid, to the alcohol, or to some other constituent, yet it is the general opinion among practitioners that the alcohol alone is the harmful ingredient. Bauer and Bollinger found in some of their cases an interstitial nephritis, but over and above the hypertrophy thus associated there were others whose cause was apparently the excess of stimulating beverages. Hirsch[1] has recently found in all his cases of hypertrophy from beer drinking an interstitial nephritis, which he supposes the true cause.

Various explanations have been offered for the hypertrophy. The action of the alcohol itself is a doubtful explanation, for on this it is difficult to explain the absence of hypertrophy in persons who frequently drink small quantities of spirits. Moreover, the immunity of the wine-drinker is often remarkable. Experimentally, alcohol has no power in animals to produce hypertrophy. It has been attributed, again, to the large quantity of assimilable foodstuffs in Munich beer; but this is improbable, for the reason that only certain persons are attacked. The real cause or causes are therefore obscure, but we may conclude that there is another factor besides the beer in the presence of arteriosclerosis, chronic nephritis, emphysema, previous infections, or overexertion.

Tobacco.—The production of hypertrophy by this drug has occasionally been described, but the evidence of such is for the most part clinical. Both dilatation and hypertrophy has been noticed. The symptoms of poisoning are the most prominent thing, and probably a timely stoppage of its use prevents the development of hypertrophy. The chief symptoms are palpitation, coming on either at rest or after slight exertion, some hyperpnœa, and occasional pain of an anginoid character.

In pituitary tumors, in which hypertrophy is sometimes noticed, we are justified in assuming that it is due to the overstimulation of the cardiac muscle by a secretion of the affected gland.

Morbid Anatomy.—With the features which distinguish the muscle of hearts hypertrophied as the result of a valve lesion, dilatation of a cavity, and so forth, we are familiar. These changes consist in an increase in the volume of each fibre, an increase in the sarcoplasm, a broadening of the fibrillæ, and an increase in size and change in form of the nucleus.

Stadler,[2] from the experimental side, has come to some very definite conclusions on the effect produced in animals as a result of artificially produced aortic insufficiency, tricuspid insufficiency, and aortic stenosis. The changes occur in those parts of the heart on which most stress falls, namely, the right auricle in tricuspid insufficiency, the left ventricle in mitral insufficiency and aortic stenosis. The fibres are markedly increased in thickness; the sarcoplasm is much increased, sometimes to such an extent as completely to isolate the fibres. In longitudinal section the spindle-shaped space which encloses the sarcoplasm is enlarged. An increase in thickness of the fibrils is sometimes obvious, but at other times not so marked, or even at times a lessening in their thickness is evident. Many forms of nucleus are found. A most important feature

[1] *Deutsch. Arch. f. klin Med.*, 1900, vol. lxviii, pp. 55 and 338.
[2] *Ibid.*, 1907, vol. xci, p. 98.

in these hearts is an increase of connective tissue, showing itself sometimes as a diffuse increase affecting a whole segment of the heart or a smaller area. For instance, in the right auricle, in tricuspid insufficiency, not only are the normal septa thickened, but between the single muscle fibres a more or less broad band of connective tissue has been developed. The connective tissue thus found is quite distinct from that so characteristic of myocarditis which is found in small areas. Stadler considers this increase of connective tissue as a reaction from the overfilling which acts so as to increase the elasticity of the walls of the cavity, *i. e.*, to diminish its distensibility. Opinions are less agreed on the presence of an increase of elastic tissue, some observers having found an increase, others no change. There is frequently an increase in the brown pigment at both poles of the nucleus.

The Increase of Muscle Cells in Hypertrophy.—Such is by no means definitely proved. Zielonko, using frogs and rabbits in whom he made an artificial stenosis of the aorta, found an increase in the fibres of the heart. This agrees with the assertion of Kölliker, Rokitansky, Zenker, and Rindfleisch, who all suppose a splitting of the fibres to form new ones. Tangl, using the same method as Zielonko, finds that only in fetal life and shortly after birth is the muscle increased by splitting.

It is somewhat early to form conclusions on the extent to which in various forms of hypertrophy the muscle fibres increase in size or number. In the physiological form of hypertrophy from work the available histological evidence points to no alteration in the size or appearance of the fibres; hence we must conclude that the increase in thickness must be due to a larger number of normal muscle fibres being present. To suppose that physiological hypertrophy, the muscle only doing extra work at special times, can be distinguished by the presence of normal muscular fibres, and the pathological or compensatory hypertrophy, where the muscle constantly does increased work, by an increase in the size of the fibre, alterations in the nucleus, sarcoplasm, etc., is a tempting hypothesis, but one for which, as yet, there is no support.

Symptoms of Compensatory Hypertrophy.—From our definition the presence of hypertrophy in itself cannot give rise to many symptoms because we have excluded all consideration of cardiac failure; nevertheless it will be advisable to mention a few, although it is difficult to say whether they are due to hypertrophy or commencing failure. Pain in the precordial region, usually of a dull type, and even true anginal attacks may occur, especially if the hypertrophy is due to disease of the coronaries or myocardial sclerosis. Various subjective sensations, such as transient giddiness, singing in the ears, or flashes of light before the eyes, may trouble the patient. On exertion, unless in well-compensated hearts with slight lesions, there may be dyspnœa.

Physical Signs of Compensatory Hypertrophy.—The appearance of the patient may present no indication; but if the hypertrophy is due to a constant high arterial pressure there may be a florid appearance and a general fulness of the tissues of the face.

Hypertrophy of the *right auricle* may show itself by a more vigorous pulsation of the veins in the neck, especially when the patient is in the

horizontal position; such may be more evident in a tracing in which the upstroke, due to the auricular contraction, can be definitely fixed. It may be possible by palpation to detect over the third and fourth ribs to the right of the sternum an impulse occurring before that of the ventricle. The contractions of the auricle normally give no sound that is loud enough to be distinguished by the ear, but when the auricle contracts more vigorously, as it does in hypertrophy, it may be possible to hear the auricular contraction either to the right of the sternum or over the pulsating jugular area in the neck.

Hypertrophy of the *right ventricle* usually shows itself by causing a slight bulging in the costal angle with definite positive pulsation, not negative as may be seen normally along the left costal border. The apex of the heart is often pushed over to the left, sometimes diffuse and never easily localized. The pulsation at the apex is usually enfeebled. The venous pulsation in the neck may be marked and the jugular pulse may be of the ventricular type.[1] Percussion may not give any reliable evidence. The first sound over the tricuspid area is loud and the pulmonary second sound is usually accentuated. The sign of enfeeblement of the right ventricle is *hyperpnœa* coming on with the least exertion.

Hypertrophy of the *left auricle* is not easy to diagnose. The apex tracing may show a larger wave than the auricular beat usually gives; it may again produce an audible sound, but this is uncertain, and some authors have claimed that when the left auricle is enlarged, especially in dilatation, there is an increase in the dulness at the left apex. A loud presystolic murmur in mitral stenosis usually means, according to Mackenzie,[2] a virgorously acting left auricle.

Hypertrophy of the *left ventricle* presents the least difficulty. On inspection there is a forcible pulsation of the chest, especially of the left side, at each heart beat, and if the patient be young, there may be some bulging of the thorax. The carotids pulsate more markedly than normally, and the apex beat, which may be in the nipple line or farther out in the fifth, sixth, or seventh spaces, is prominent and fairly easily localized. To the hand the apex beat is more forcible than normal and longer in duration. Gibson[3] described a quivering or "shuddering" sensation which is given to the hand. The first sound at the apex is louder and longer, but with some loss of compensation; the sound may be short and sharp, and at the tricuspid there may be a doubling of the first sound. The aortic second sound is accentuated. The pulse is usually full and strong, or if the tension is high from renal disease, it may be hard between the beats, with strong but not large beats.

In the diagnosis of all forms of cardiac enlargement, the *x*-rays are of great service; when the heart area can be mapped out accurately on a screen and measurements made and compared with those of the normal, such must be the final appeal in matter of enlargement. But it affords no clue whether the enlargement is due to dilatation or hypertrophy, which must be determined by summing up the other evidence.

[1] Mackenzie, *The Pulse*, London, 1902, p. 95.
[2] *Quarterly Journal of Medicine*, 1907–08, vol. i, p. 39.
[3] *Diseases of the Heart and Aorta*, Edinburgh, 1898, p. 743.

The Blood-pressure in Hypertrophy.—In the young athlete with a perfectly balanced circulation, it is unusual to find a high maximum or minimum blood pressure during rest; in fact, comparing young men of the same age and standing such as one finds at the universities, those who take violent exercise, as a rule, have blood pressures somewhat lower at rest than those whose pursuits are more sedentary. During exercise the blood pressure rises considerably at first, but later on, with the onset of cutaneous hyperemia and perspiration, the minimum blood pressure is often found below normal. The records of the blood pressure in cases in which hypertrophy is the result of an abnormal condition are different. The cause here, whether nephritis, a valvular lesion, an overstrain, etc., instead of being intermittent, as in the athlete, is constant; the heart has continually to do more work to overcome the obstacle to the circulation, and, as a consequence, if there is good compensation, the blood pressure is continually higher than normal. The records of the blood pressure in renal disease, in arteriosclerosis, and in aortic disease need only be mentioned as examples.

When such an hypertrophied heart begins to fail the blood pressure may fall, but the height of the blood pressure is no evidence of the condition of the patient, for a patient whose blood pressure had dropped to 150 mm. from 200 mm. would be in a much worse plight than one whose blood pressure dropped to 120 mm. from 150 mm.

CHAPTER VII.

INSUFFICIENCY AND DILATATION OF THE HEART.

By ALEXANDER G. GIBSON, M.D., F.R.C.P.

Theoretical.—Cardiac insufficiency is produced by any interference with the heart as a whole or any of its essential parts, preventing a proper discharge of its functions. Such changes are entirely independent of hypertrophy, though this may occur coincidently; in fact, hypertrophy is the property which combats interference with function; as Fräntzel has said, *hypertrophy is the guarantee of life.* Cardiac failure, therefore, may occur in a hypertrophied or non-hypertrophied heart.

For an adequate knowledge of any condition of cardiac insufficiency it is necessary to know exactly the effect of the particular agent causing the failure on each particular function of cardiac muscle. Much light has been thrown on the conditions of heart action by the application, to the study of the human heart, of the researches of Gaskell and Englemann on the five functions of contractility, excitability, stimulus formation (rhythmicity), conductivity, and tonicity. It is clear that when different agencies act on heart muscle, the interference with these functions is not necessarily the same in all cases, and our knowledge to be adequate should include the effect of the cause on each one of these functions. Moreover, certain parts of the heart itself have particular functions more than other parts, thus rhythmicity is most marked at the mouths of the great veins, and least in the ventricles. We know that certain forms of irregularity of heart action are connected with a failure of one or more of these functions. Thus *pulsus alternans* is now associated with a failure in the function of contractility, and other conditions are associated with a loss of conductivity, such as in Stokes-Adams disease, and the irregular pulse of mitral stenosis.[1] The instances in which interference with certain functions can be affirmed with accuracy are chiefly those in which perhaps only one of the functions is affected in a manner sufficiently marked to be obvious to clinical methods. In the great majority of cases of heart failure, however, we can only guess as to the state of the various functions.

So far as can be at present predicted it is possible that cases of sudden cardiac failure may belong to a class in which the functions of contractility, excitability, or rhythmicity may be at fault. For instance, if one considers the sudden death that occurs in cases of aortic disease, it is probably due to a failure of contractility for the time being. Again, the sudden death that occurs in fatty degeneration of the heart is probably of the same nature. Accurate knowledge of these conditions is as yet not forthcoming and such suggestions are merely guesses.

[1] Mackenzie, *Quarterly Journal of Medicine*, Oxford, 1907, vol. i, p. 39.

We are better acquainted with conditions of interference with conductivity, because this function, at least in certain parts of the heart, is abnormally developed in certain fibres. In the matter of transference of the stimulus from auricle to ventricle the length of time between the auricular and ventricular impulses, usually one-fifth of a second, serves as a guide to the state of this function. Certain researches suggest that it may be possible to detect alterations in this function, even in the auricles themselves. The stimulus of each contraction begins in all probability in that part which corresponds to the sinus venosus; this stimulus can be transmitted to the auricular node either by the auricular muscle or directly by the sino-auricular bundle of muscle fibres; it may therefore be possible in the future to distinguish between several forms of interference with conductivity.[1] Mackenzie suggests such a one is the irregularity coming on in mitral stenosis, the dilatation of the auricle being such as to prevent muscular conduction from the great veins to the ventricle, in whose absence the rhythm is taken on by the conducting system nearer the ventricle. Tonicity, again, is a function which in some cases of cardiac failure is probably one of the chief factors at fault. This, however, will be discussed under Dilatation.

By far the greater number of causes which give rise to cardiac failure are due either to a mechanical interference with the action of the muscle or an anatomical change in the muscle fibres themselves from intoxication, inflammations, etc. In these there is probably an impairment of all functions at the same time, though not necessarily in an equal degree. Under the first class would be included conditions of cardiac failure from valvular defects, overexertion, resistance to the flow of blood in an arterial stem, etc., and under the second the numerous interferences with cardiac muscle such as occur from inflammations, degenerations, parasites, new growths, etc. A limit should be given to the term cardiac insufficiency for the purposes of description, although of necessity there are no definite lines of demarcation between sound and unsound hearts. A normal heart is one whose reserve power is capable of sustaining a large amount of extra exertion without damage to its structure or size. When any cardiac impairment is present such additional exertion is not possible without distress. The average person who does not take even moderate daily exercise has a lower limit of cardiac endurance than the person who is so accustomed. Another class of patient, even if he walks a yard or two, has breathlessness or some other symptom, but when reclining in bed is comfortable. In the severest type of insufficiency there are symptoms even when at rest, with œdema and orthopnœa, such as are seen in the last stages of chronic heart disease. For clinical purposes such a subdivision as has been indicated is necessary, for it gives at once the lines along which treatment should proceed. Regarded in a slightly different way, these various classes may be looked upon as having different amounts of reserve power; the one in whom symptoms are present only on the severest exertion having the most, another in whom symptoms are present even when at rest having no reserve power at all. This lack

[1] Keith and Flack, *Journal of Anatomy and Physiology*, 1907-08, vol. xli, p. 172.

of reserve power may be brought about in two distinct ways: in one the requirements of the heart may increase even for the resting condition, such as happens when a valve undergoes increasing erosion, or when, as the result of overexertion, the cavity of the heart dilates; in the second, with a normal amount of work to do, the power of the heart to do that work steadily diminishes; this form occurs in febrile conditions, in inflammations and degenerations of the heart muscle. In practice, probably the two forms frequently occur together, for when a heart is dilated, and the walls stretched, the blood supply is of necessity poorer than if the heart were not subjected to such stress.

DILATATION OF THE HEART.

Theoretical Considerations.—The term dilatation of the heart is so firmly established, both in clinical medicine and morbid anatomy, that any description of chronic cardiac failure without a reference to it would be incomplete. So intimately is it associated with certain forms of cardiac insufficiency that the consideration of dilatation of the organ almost usurps that of the other functions. In its clinical sense the term is applied to conditions of heart insufficiency in which the main feature is an enlargement of one or more of the cavities of the heart with an enfeeblement of function; in morbid anatomy the term is applied to any enlargement of a heart chamber. The two definitions are by no means co-extensive, for a cavity may be enlarged and yet give rise to no interference with function because a concomitant hypertrophy may be the means of making the organ again effective. Such dilatation would be compensatory, and the term cardiac insufficiency could no longer be applied to it. These cases would come under the pathological variety of hypertrophy, which has already been discussed. In the dilatation which is pathological, in that heart failure accompanies it, the cavity of the heart is enlarged to such an extent that the normal pressure per unit area, owing to stretching, cannot be communicated to the heart contents. Such a condition may be the result of two main causes: in the first there is a progressive or sudden dilatation of the cavity by mechanical causes in which the force of the heart remains the same, which having to act on a greater surface area is not able to give the necessary pressure to the contained blood. This condition, while it leads to stimulation of the heart muscle at first, ultimately produces, either by excessive stretching or by altered nutrition from lack of blood supply, an enfeeblement of the muscle fibres themselves and consequent loss or enfeeblement of their contractile power. The second is that in which, without any alteration in the mechanical conditions, an alteration in the power of resistance or elasticity of the cardiac muscle takes place, by interference either with its nutrition and functions, or the latter alone; the cavity then dilates as a result of the normal pressure exerted on it.

To follow up the mechanical conditions of dilatation a little further—considering the course of events in a case of mitral regurgitation—the left auricle during systole receives back a certain volume of blood which it had previously given to the ventricle; in addition to this it receives

the normal or nearly the normal amount from the pulmonary veins. This extra amount of blood is easily accommodated in the auricle by dilatation from simple stretching. This causes a stimulation of the muscle of its walls and is the stimulus for an increased force being expended at the systole of the auricle, with the result that the ventricle receives the normal amount of blood, together with the extra amount which is thrown back during systole of the ventricle. The circulation is now in a condition of equilibrium again, and supposing that no interference with the nutrition of the heart muscle occurs no loss of balance is likely to occur if the extent of the valve lesion is constant. But supposing the valvular defect increases, the balance between the force necessary to drive the total amount of blood in the auricle into the ventricle and that which it is possible for the auricle even in its stimulated and hypertrophied condition to exert is lost, and the blood accumulates in the auricle and leads to further dilatation. Under these conditions of stretching, it is not possible for the muscle fibres to receive their proper nutriment and a condition of fibrosis results.

The second series of conditions under which dilatation is produced is more obscure—namely, the dilatation that accompanies the degeneration of muscle fibres of the heart. The most marked examples of this are seen in fatty degeneration, and sometimes in the degenerations which accompany fevers. In this class would be included those interferences from inflammation of the muscle—including parasitic irritation—and from new growths. It would be most rational in this class to suppose that the normal pressure during diastole and a lessened resistance to contraction of the muscle produce the same conditions as a heightened diastolic pressure and a greater demand on the contractility of the heart do in the normal condition of the fibres.

So far we have considered dilatation of the heart from increased resistance to contraction, or increased stretching during diastole, and from lesions of the muscle itself; but there is a large class in which the dilatation depends on a direct action on one or more functions of heart muscle acting either in a chemical manner through the blood or through the nerves. Such action, we presume, is not an interference with the muscle cell as a living structure but a pure interference with certain particular functions. The function of heart muscle which in this connection would attract most notice is that of *tonicity*. Bauer,[1] in 1893, was the first to suggest that certain forms of dilatation were due to a diminution of this function, and Herz[2] and Gossage[3] have attributed certain conditions to an interference of the same. We have no method clinically of estimating the condition of tonicity, so that as yet proof of the hypothesis is some way off; yet certain considerations make it very probable that changes in tonicity may be so marked as to produce great interference with heart activity. The heart of *Emys europæa*, or land tortoise, has been shown by Fano to possess in addition to the ordinary rhythmical contractions a slowly developing and slowly subsiding contraction which, when it

[1] *Festschrift f. Pettenkofer*, 1893.
[2] *Deutsch. med. Woch.*, 1900, xxvi, 128 and 148.
[3] *Lancet*, 1906, vol. ii, p. 1126.

appears, has the ordinary contractions superimposed on it. Again, Ebstein[1] records the observation that stimulation of an exposed non-beating heart with a point of a scalpel was followed by a relaxation of the heart and dilatation of its cavities which was succeeded by an active contraction. Gossage, in speaking of the affection of this function by drugs rightly considers that digitalis increases tonicity, while lactic acid diminishes it. Supposing the tonicity of heart muscle to fail, the heart wall is more flabby than normal and easily receives the inflowing blood during diastole; a normal systole of such a heart will not be sufficient to empty the cavity completely, with more forcible contractions the cavity is emptied as well as before, and the circulation is undisturbed. If from degeneration of the muscle fibres contractility cannot be increased, then there is dilatation and consequent enfeeblement. Supposing contractility alone fails, the pressure in the aorta lessens, and if all the chambers suffer equally, less blood therefore enters the ventricle and the heart merely beats more feebly without undergoing dilatation. If both contractility and tonicity were to fail simultaneously there would be little if any dilatation. In the purely mechanical origin of dilatation, such as occurs from overexertion, both tonicity and contractility oppose themselves to dilatation until from stretching, lack of proper blood or fatigue, tonicity begins to fail. Fatigue of muscle, as is well known, is accompanied by the production of an acid reaction due to sarcolactic acid, which is potent to produce a lack of tonicity.

Taken in conjunction with what will be said on chronic cardiac failure, it is evident that dilatation of the heart cannot be taken to mean the same as cardiac insufficiency. Dilatation does no doubt accompany many forms of heart failure, but the latter is the important thing and the dilatation is merely a physical sign in the course of the ailment. It is by no means desirable, however, to do away with a term of so much significance in clinical medicine. It would be well perhaps to give a little more exactness to the term, by speaking of cases of cardiac failure with dilatation rather than of dilatation alone.

The accompanying synopsis gives the conditions in which dilatation of the heart is most frequent:

1. From a direct interference with one or more of the primary functions of heart muscle, the function of first importance being that of tonicity.
   - (*a*) From drugs and toxins, tobacco, beer, diphtheria toxin, etc.
   - (*b*) From nervous action, *e. g.*, the sudden dilatation from physical disturbance.
2. Most causes of chronic cardiac insufficiency.

CARDIAC INSUFFICIENCY

Acute Cardiac Insufficiency.—Etiology.—(*a*) *Wounds of the Heart.*—These may be direct by a sharp instrument, or indirect from a crush causing a fracture, or from a crush alone. It is not necessary that the wall of the heart should be penetrated. Such cases as show only a very

[1] *Ergebnisse der Physiologie*, 1904, p. 168.

small wound have been examined for the presence of fatty degeneration or other abnormality of cardiac muscle without success. Experiments have been undertaken which show how difficult it is to wound the heart by blows if the pericardium is intact, whether the heart is filled or not. The extent of the rupture is in no sense proportional to the symptoms or the length of time which such a patient survives; small wounds may be fatal in a few hours and with moderately large ones the patient may survive several days. Cases in the literature are by no means rare in which the heart wounds have been stitched and the patient recovered. The heart failure caused by wounds cannot wholly be due to mechanical interference with heart action, for the degree of heart failure would then probably show some relation to the size, depth, and position of the wound.

The phenomenon of *fibrillation* of the heart so frequently observed in experimental animals undoubtedly must occur in human beings, but owing to difficulties in diagnosis we are as yet ignorant of the circumstances under which it occurs. From the analogy of animal experiment we are justified in assuming that fibrillation can occur from electrical, mechanical, and chemical stimulation. Kronecker and Schmey[1] found that by stimulation of the interventricular septum of the dog's heart at the junction between the upper and middle thirds the whole heart could be thrown into fibrillary contractions. They attributed the effect to the destruction of a coördinating centre in the septum. No proof of such a centre has ever been obtained: there is no nervous tissue in that region in greater amount than in other parts, and no stimulation of special portions of the heart where nervous tissue is known to exist or of the entering nerves themselves has been found to cause fibrillation. The two sides of the ventricular septum, as will be described later, are the sites where the two limbs of the bundle of His diverge in their course to supply the muscle of the right and left ventricle. It is questionable whether, from the definite localization of the point according to Kronecker, we are dealing with a lesion of this important part of the cardiac musculature. Electrical, especially faradic stimulation, and chemical stimulation, as, for instance, by perfusing the coronary arteries with a solution of potassium bromide, easily cause fibrillation. The fact that recovery can occur to some extent from all stimuli shows that the hypothesis of the destruction of a coördinating nerve centre is insufficient. Two other conditions, probably alike in their effect on cardiac muscle—namely, tying a coronary artery and the injection of suprarenal extract—are potent to cause fibrillation. The relation between fibrillation and the nutrition of the muscle is therefore close, and we may suppose, in the want of further proof, that the mechanical, chemical, and electrical stimuli cause constriction of the coronary arteries supplying special areas. Stimulation of the skin produces in certain persons a local pallor due to vasoconstriction, and the same mechanism may also be present in the cardiac muscle. But as in the skin a stimulus sometimes produces a local vasodilatation not preceded by any vasoconstriction, so there may be such differences in the heart which may explain the inconstancy in the appearance of fibrillation from certain stimuli, *e. g.*, faradization.

[1] Quoted by MacWilliam, *Journal of Physiology*, Cambridge, 1887. viii, 296.

A third danger from heart wounds lies in the amount and rapidity of the accumulation of blood in the pericardium and probably whether such remains in the pericardium or has exit into the pleura. Certain conditions affect the bleeding: a small wound, owing to its position or smallness, may be completely occluded during systole; pressure against the sternum or thoracic wall and quick thrombus formation may limit the hemorrhage. A long period of collapse favors thrombus formation, and anything, such as overexertion, which increases the blood pressure, may prove suddenly fatal. The effusion of blood, if its amount does not interfere with the heart's action so as to cause death, and failing an infection from without, undergoes absorption to some extent; an adhesion, partial or general, of the two layers of the pericardium results.

(*b*) *Spontaneous Rupture.*—The question whether a sound heart ever ruptures must probably be answered in the negative. The more carefully cases of spontaneous rupture of the heart are examined, the more often definite, although perhaps minute, changes in the muscular wall, which have caused a weakening of resistance at the site of the rupture, are found. The commoner causes of such rupture are infarcts and areas of softening of the heart muscle which are caused by stoppage or partial closure of the coronary arteries, small cicatrices, myocardial abscesses, foreign bodies (needles, etc.), echinococci; localized fatty degeneration, and sclerosis of the coronaries in connection with brown atrophy of the muscle have also been described.

The site of the change, whether inflammation or degeneration, is a weak spot; with the pressure during systole the area becomes stretched and, varying with the elasticity, sooner or later an aneurism appears and finally a rupture occurs. Small aneurisms of apparently little significance can often be seen on the auricles of hearts from old persons; they appear as dilated pouches in between the trabeculæ somewhere near the auricular appendix, and the substance of the dilated portion is apparently only formed of endocardium and epicardium.

As a rule, the site of the rupture is obviously related to some underlying change in the cardiac muscle. The canal leading outward may fork and open into the pericardium by two orifices. The pericardium is usually filled with blood. The condition, according to some recent statistics, occurs most frequently in men between sixty and sixty-five years of age.

Rupture of Valves.—A number of cases of valve rupture, especially of the aortic valves, have been recorded. Such occurs most commonly in valves already slightly damaged by atheroma; and if the valve is more damaged, even slight exertion may bring on rupture.

(*c*) *Rapid Effusion of Blood into the Pericardium.*—Cohnheim showed, in 1882, that an injection of oil into the pericardium caused a lowering of arterial blood pressure with an increase of that in the veins. Such fluid in the pericardium acts probably by lessening the capacity of the heart to take in fluid and thus lessens its output.[1]

Three clinical conditions are associated with a rapid effusion of fluid

[1] See the work of A. Herz, Lubarsch and Ostertag's *Ergebnisse der Pathologie*, 1903, ix, 852.

into the pericardium: the bursting of a cardiac aneurism, of an hydatid cyst, or the rapid transfusion of fluid in an acute inflammation. The grade of heart failure bears no marked relation to the amount of fluid; it is more dependent on the rapidity of formation, for with a slowly formed effusion more opportunity is given for the pericardium to relax and the pressure with a given amount of fluid is not therefore so great. Cohnheim found that a pressure of 300 mm. of saturated magnesium sulphate solution could be supported in a dog.

(*d*) *Overexertion.*—To anyone acquainted with some of the severer tests of endurance in athletic contests cases of heart failure are not rare. The story of the messenger from the battlefield of Marathon who fell dead after delivering the news of victory is a good example of a severe case of sudden left heart failure ending in death. In many races men come in pale and perhaps faint immediately after finishing. The failure of heart action affects one or both sides of the heart; if the aortic blood pressure is lowered by feebleness or asystole of the left ventricle, then loss of consciousness or a feeling of dissolution comes on, and if the same happens for the right heart the effect is to cause a great amount of dyspnœa, which is increased by the slightest exertion. The two ventricles may fail simultaneously, with the result that in addition to a feeling of faintness there is also great dyspnœa.

Acute failure may come on during the course of chronic failure or even when all objective signs of failure have disappeared. Two cases reported by Rieder[1] (Case II and Case III) are important in this respect. The first died suddenly after leaving the hospital with no subjective or objective symptoms; the second died suddenly in the course of a chronic heart failure.

(*e*) *The Presence of a Large Amount of Air in the Heart.*—Two sources have probably to be taken into account: First, air which has entered by the veins, and of these the neck veins and the uterine veins after parturition are the most important; secondly, the formation of free gas in the heart during decompression after subjection to high pressures. The first is a danger which has long been taken into account in neck operations, especially in tracheotomy. The patient is in a condition of marked dyspnœa and the inspiratory negative pressure in the neck veins is much greater than during the normal inspiratory phase. Air, when it enters a wounded vein, goes to the right side of the heart, where it hinders the proper onflow of blood into the pulmonary artery. It may occasionally be found on the left side of the heart, having come from the right side through the lung capillaries.

(*f*) *Heart Thrombi.*—The number of cases of heart failure from this cause is extraordinarily small. Pawlowski collected all the cases recorded and they only come to 25, of which 19 were in the left and 4 in the right ventricle. Such thrombi are frequently of the size of a large walnut and are often attached to some portion of the heart wall or valve; hence the name polypi. They may be the cause of death in persons with no suspected disease or in diseases such as typhoid fever.

[1] *Deutsch. Arch. f. klin. Med.*, 1895, vol. lv, p. 21.

(*g*) *Sudden Obliteration of a Large Section of the Lung Arteries.*—Experimentally, Lichtheim found that three-quarters of the lung arteries could be tied without producing any lowering effect on the carotid blood pressure. These experiments have been modified somewhat of late. Lichtheim used curarized dogs with opened thorax. If a young dog be used and the left pulmonary artery tied without opening the pleura, the carotid pressure falls, in one case of Landgraf's[1] from 70 mm. to 30 mm. As with all the other causes of heart failure hitherto dealt with, the more sudden the change the greater the failure, and *vice versa*. The symptoms are necessarily those of a right-sided heart failure, marked increased rate of breathing, cyanosis, unconsciousness, etc.

(*h*) *Sudden Interference with the Coronary Circulation.*—This is most commonly the result of atheroma, thrombosis, embolism, or a spasm of the muscular walls. Cohnheim showed that after tying a coronary artery that part of the heart supplied by the vessel went into fibrillary contractions. It is doubtful whether a human being could survive such a serious interference with cardiac nutrition, but a gradual obliteration can be sustained. Thrombosis is comparatively rare except as a final stage in angina pectoris. A number of cases of embolism have been described. They are usually the result of atheroma, acute non-malignant endocarditis or malignant endocarditis. The embolism usually affects the right branch of the coronary artery; hence right-sided heart failure is common with cyanosis.[2]

(*i*) *Mechanical Interference with the Heart, e. g., Asphyxia.*—Sudden asphyxia occurs clinically under a number of conditions. It may occur as the result of external interference, such as strangulation, or from an obliteration, partial or complete, within the air passages, such as a foreign body in the pharynx or larynx, œdema of the larynx, œdema of the lungs, or spasm of the bronchial muscular apparatus. The postmortem appearances are well known; they consist in an enormous engorgement and dilatation of the right side of the heart, especially of the right auricle.

The increase of carbon dioxide in the blood stimulates the cardiac, respiratory, and vasomotor centres in the medulla and the cardio-accelerator centre in the cord. In the first stages we have, therefore, a slower heart beat, although more forcible from spinal stimulation, a greater respiratory activity, and an increase in blood pressure. The more forcible inspiration increases the filling of the right heart and lung vessels, and the more forcible expiration increases the venous pressure and the emptying of the left heart. The brunt of the interference tends to fall on the right side of the heart because inspiration tends to fill it and the lung vessels, but expiration tends to empty only the left side and not the right; moreover, the walls of the right auricle and ventricle, being thinner, tend the sooner to yield to the increased internal pressure. During the first stage the most important features are the accelerator action on the heart increasing the force of the beat, the inhibitory action slowing the beat, an increased venous blood pressure, and an increased

[1] *Zeit. f. klin. Med.*, 1892, vol. xx, p. 181.

[2] v. Oestreich, *Deutsch. med. Woch.*, 1896, vol. xxii, p. 148, where the literature previous to that date is given; also v. Barth, *Deutsch. med. Woch.*, 1896, xxii, 269.

arterial pressure. During the second stage the inhibitory centre becomes fatigued, the heart is becoming dilated; hence more force is necessary to expel the contained blood; therefore, the accelerator action does not have its proper effect as it does if the right side of the heart is emptied, as can be seen experimentally or clinically when a very cyanotic patient with heart failure is bled. The arterial blood becomes more and more venous, and does not properly nourish the muscle of the walls; hence another source of dilatation is present.

(*j*) *Interference of the Heart from Infections.*—Sudden death is by no means infrequent in the course of some of the severer infectious diseases. Perhaps the one in which it is most frequently seen is diphtheria, but sudden death may also occur in scarlet fever, typhoid fever, pneumonia, smallpox, rheumatic fever, and septicemia. The explanation is not always easy. In all acute infections there are changes in the heart muscle, usually of the nature of cloudy swelling and sometimes of actual myocarditis, but the myocardial changes seem to be insufficient to account for the sudden death. In diphtheria, again, a parenchymatous change of the nerves and in particular of the vagus has been found.

(*k*) *Poisons.*—In this place may be mentioned heart failure as the result of certain drugs, for instance, phosphorus and pilocarpine.

(*l*) *Interference with the Nerves of the Heart.*—The vagus is the nerve by which the functions of the heart are restrained. We are probably justified, in view of experiments, especially those of Engelmann, in believing that the vagus contains groups of fibres which act on special functions. Thus, Engelmann has proved that under certain circumstances a pure effect can be obtained on the function of contractility.

We cannot, however, go further at present than to say that in cases of heart failure from nervous interference it is probably the vagus through which the stimulus is conveyed, and this may have its origin either in the peripheral terminations of the nerve (as with pilocarpine), in the nerve itself, as from a tumor in the neck, in the vagal centre, as in certain cerebral tumors, or at the peripheral end of fibres which convey afferent impulses up to the vagus centre. Probably afferent fibres ending in the vagus centre are supplied to several organs. Injuries to the abdomen frequently produce some heart failure and injuries to the larynx are sometimes fatal. Attention has been called to the sudden death caused occasionally by thoracic paracentesis, probably from sudden and severe afferent stimulation of the vagal fibres in the lungs.

Some Types of Sudden Cardiac Insufficiency.—*Sudden Rapidly Fatal Heart Failure from Paracentesis Thoracis.*[1]—A female, aged eight years, had symptoms which pointed to the presence of fluid at the base of the right lung. "On June 14 it was decided to explore the affected area, and an aspirating needle was accordingly inserted in the ninth intercostal space, one and one-half inches from the spine, for a depth of about two inches; no fluid was obtained and only a drop or two of blood. Only one puncture was made, and the whole process took about one minute. A small amount of frothy blood appeared at the mouth and nose. Immediately

[1] Russell, *St. Thomas' Hospital Reports*, 1899, vol. xxviii, p. 465; see also Capps.

after the withdrawal of the needle the child was observed to have lost color, or rather to have a livid appearance, with a strong, double-convergent squint, and some rigidity of the arms. The pulse could not be felt and the heart sounds were inaudible. Ether, brandy, and strychnine were injected subcutaneously, and two pints of normal saline were infused into the femoral vein. Breathing continued irregularly for a minute or two, the respirations being slow and gasping, then ceased. Artificial respiration, which was kept up for half an hour, was of no avail, although perhaps for five or six minutes it evoked spontaneous attempts at breathing. The pulse could not be felt after the onset of symptoms." No change was found in the heart at the postmortem examination. It is not unusual in these cases, if life is prolonged further than in that quoted, to see convulsions followed by hemiplegia.

Sudden Death from Thrombosis of the Pulmonary Artery.—"Male,[1] aged twenty-four years, with moderately severe attack of typhoid fever. In the middle of the second week a fatal termination occurred under the following circumstances: At the evening visit the patient was quite well, cheerful, and had no pain. The pulse, however, and the apex beat were intermittent without being especially weak; the intermission followed regularly after the second or third pulse beat. The pulse was 80, not reckoning the failure of beats. The patient was quiet until 11 P.M., and slept well. At this hour he awoke, asked for a bedpan, and passed a somewhat profuse, liquid stool without any difficulty. He also took a urine glass and passed fifteen ounces of urine. He had scarcely done this and spoken a few words to his neighbor, when he suddenly made a few strokes with his arms, took a few deep, snorting breaths, and after a few minutes died." A plugging of a main branch of the artery supplying the inferior lobe of the right lung was found.

Right Heart Failure.—Clifford Allbutt relates the following.[2] "In the summer of 1868 I began to walk in the Alps a little too soon for good training. . . . . I was suddenly seized with a strange and peculiar *besoin de respirer*, accompanied by a very distressing sense of distension and pulsation in the epigastrium. On placing my hand over my heart I felt a laboring, diffused beat all over the epigastrium. I at once opened my shirt, and ascertained by percussion that the right ventricle was very greatly dilated. I therefore threw myself at length upon the grass, with my shoulders raised, and had the satisfaction in a few minutes of finding the distension, the oppression, and the dulness recede. I was then able to rise and sit down, or even to move about on the level; but, curiously enough, the instant I began to ascend, the symptoms returned. I was therefore obliged to send K. forward and proceed myself with great caution. When I got up to the height of the inn, and had only to walk a mile or two on the level by the waterway, I ceased to suffer, as I felt no general fatigue whatever, and was able to dine well on my arrival. In the night, about 3 A.M., I was suddenly awakened by a

[1] Quoted by v. Jürgenson in Nothnagel's *Specielle Pathologie u. Therapie*, vol. xv, Band i, from Virchow.

[2] *St. George's Hospital Reports*, London, 1870, vol. v, p. 29.

severe and distressing palpitation in the epigastrium, with great dyspnœa; there was not, however, the same extension of dulness over the sternum. I went to the window and drew a few long respirations, which gave me ease, and I lost my ailment altogether. No doubt the pressure of a full abdomen against the diaphragm, while recumbent, had again embarrassed the overtaxed right ventricle."

Chronic Cardiac Insufficiency.—Etiology.—(*a*) *Lesions of the Heart Muscle.*—These include malnutrition from insufficient or unsuitable food, wasting from new growth or diabetes; degenerations, such as cloudy swelling, fatty degeneration, amyloid degeneration; the effects produced by infections, such as diphtheria, rheumatic fever, pneumonia, influenza, etc.; new growths of the heart muscle itself; parasites of the heart, and coronary artery disease.

(*b*) *Lesions of Valves.*—These are described in another section.

(*c*) *Lesions Peripheral to the Heart Itself.*—The causes under this head group themselves naturally into two, according as the lesion lies in the *pulmonary* or *aortic* arterial tree. In dealing with hypertrophy of the heart it was mentioned that a lesion of the lungs causing an obliteration of part of the blood path in the lungs could produce hypertrophy of the right ventricle. Hypertrophy of the right ventricle is the natural reaction to a lesion opposing a proper outflow from the pulmonary artery, but if the limits of hypertrophy have been attained, or if the lesion comes on so suddenly that there is no time for hypertrophy to develop, then the ventricle must become overfilled and the contractions fail. Emphysema, bronchitis, asthma, sclerosis of the lungs, kyphoscoliosis, deformities of the chest, and mitral disease are the most frequent cause of right-heart failure. As in hypertrophy, the left ventricle enlarges from aortic disease, atheroma of the aorta, arteriosclerosis of the smaller vessels, especially in the splanchnic area, and from renal disease; all these conditions may produce cardiac failure sometimes with and sometimes without hypertrophy.

Hypertrophy of the right ventricle in lung disease may be adequate to carry on the circulation for some time, but when the right heart fails, diminution of the blood flow through the lungs occurs, the blood is insufficiently oxygenated and contains more carbon dioxide than normal, and shortness of breath comes on even at rest. With every additional claim on the heart, especially the slightest exercise, the distress is increased. The feebleness of the right ventricle shows itself in a diminution of the intensity of the pulmonary second sound, cyanosis and overfilling of the systemic veins, enlargement of the liver, albuminuria and œdema. If compensation is again established, such patients may live a tolerably comfortable life if they avoid exertion of every kind; but the slightest increase in the demands on the right heart may precipitate another attack and an attack of pneumonia or bronchitis, or indeed any infection, is particularly dangerous. In some cases such a heart insufficiency is brought on without any special antecedent; here it is probable that the balance between hypertrophy and an increasing obstruction in the lung arteries which hitherto has been maintained is now upset by the failure of the hypertrophy.

Emphysema of the lungs, which is preëminently one of the conditions giving rise to this form of cardiac failure, also causes trouble in the left side of the heart. It is difficult to see how such can be accounted for from any effect of the lung condition; it is probably to be sought in the sclerosis of the small systemic arteries, especially those supplying the myocardium, which invariably accompanies emphysema.

The three conditions which affect the left side of the heart chiefly are so similar that they may be taken together—namely, *renal disease*, particularly the granular, contracted form, *arteriosclerosis*, especially of the splanchnic vessels, and *atheroma of the aorta*. All three are associated with a high blood pressure in the stage when hypertrophy is adequate to carry on the circulation. As soon as this fails or some unfavorable condition affects the heart muscle, or an extra amount of exertion requires greater stress, the tension is lowered; the heart beats strongly, but not with its former vigor; the second sound in the aortic area is lessened in intensity; gallop rhythm is present, and the pulse becomes less hard, although probably greater in volume. The face, which previously perhaps was a good color, becomes paler and the patient often complains of drowsiness. With this the urine becomes less in amount; some swelling of the legs, enlargement of the liver, and disturbance of alimentary functions appear.

In the later stages the type of heart failure differs little from that produced by left-sided valvular disease, the diagnosis indeed between the different conditions being extremely difficult.

(*d*) *Interference with the proper movements* of the heart, as in adherent pericardium.

Heart Insufficiency the Result of Goitre.—With any obstruction to the proper air entry and outlet there comes an increased pressure in the lungs during expiration, which is communicated to the blood in the vessels of the lungs, and as a consequence the pressure in the right side of the heart is greater. This leads to hypertrophy and finally to failure of the right heart. In addition to the mechanical changes in the blood-vessels, the increased pressure, as has been determined by postmortem examinations, leads to emphysema of the lungs, which again reacts upon the right heart in the manner previously described. The longer the difficulty of breathing the greater the changes. Degenerative processes in the muscle of the right ventricle are usually found, and consist of hypertrophy with fatty degeneration. During life, according to Kraus, these patients belong to two groups: First, those with increased activity of the heart and increased frequency of the pulse, with or without subjective disturbances; secondly, those in whom there has been a longer course, who have an apex beat outside the nipple line and an increase in percussion dulness, especially toward the left.

(*e*) *Excessive Stimulation of the Heart.*—Under this title we include the heart failure from excessive exercise, the rare cases from excessive venery or worry, and perhaps also that occurring in Graves' disease.

We have seen that overexertion is responsible for hypertrophy of the heart and for acute cardiac failure. It is beyond doubt that persons who have to do hard manual labor often suffer from heart failure severer in

type and earlier in onset than those who live a more sedentary life. Clifford Allbutt pointed out the frequency of heart failure in the Sheffield foundrymen; workers in the Cornish mines and in the Glasgow shipbuilding yards have been found to suffer in like degree from overstrain. Dwellers in mountainous districts die more frequently from heart disease than those in the lowlands; as an example of these, Münzinger's[1] article on the "Tübingen Heart" may be cited. But the exact value of the factor of overexertion in these cases is more difficult to fix. Not all persons suffer from overexertion even in the areas where heart affections are most common. The patients come from the hospital class, and malnutrition may be a factor. This is especially so in Tübingen, where the diet of the peasants is poor. In highly populated centres the possibility of alcohol and syphilis requires careful elimination. Further, even though the former factors are not valid, a previous infection, such as rheumatic fever (even one of its slighter forms), diphtheria, pneumonia, influenza, or typhoid fever—all have their own effect in interfering with the structure of cardiac muscle at the time, and therefore lessen its reserve power later in life.

Von Leyden[2] thus classified the effects of overexertion on the cardiovascular system:

I. (*a*) Atheroma of the aorta.
(*b*) Arteriosclerosis.
II. Rupture and insufficiency of the aortic valves.
III. Pure cardiac failure (muscular).

Atheroma of the aorta and arteriosclerosis have been referred to; we may mention that there is some possibility, from recent researches, that both these conditions may result from the increased aortic and peripheral pressure which occurs during exertion. All drugs which produce an increase in blood pressure produce atheroma of the aorta experimentally and, the more powerful the drug to cause to rise in arterial pressure, the more does it cause changes in the aorta.[3]

Rupture of the aortic valves is a serious condition produced by great momentary overexertion. The onset of symptoms is very sudden and the symptoms themselves very alarming; they are those of a very severe aortic insufficiency. Insufficiency of the aortic valves coming on slowly, with progressive enlargement of the heart, is discussed elsewhere.

The effects of exertion on the heart have been studied by means of the *x*-rays. Taking normal, healthy, athletic men, there is agreement that hard exercise for a short time is not productive of any change which can be attributed in any sense to a dilatation of a cavity. Lenhoff and Levy-Dorn[4] examined the hearts of wrestlers before and after wrestling for a period of ten to thirty minutes. They found that to percussion there was a slight increase in the heart area, but by the *x*-rays the whole heart was lowered from descent of the diaphragm, and, apart from a very slight increase in the convexity of the right boundary line of the heart figure, no change could be detected.

[1] *Deutsch. Arch. f. klin Med.*, 1877, vol. xix, p. 449.
[2] *Zeit. f. klin. Med.*, 1886, vol. xi, p. 111.
[3] Rickett, *Journal of Pathology and Bacteriology*, 190?, vol. xii, p. 15.
[4] *Deutsch. med. Woch.*, 1906, Jahrg. xxxi, p. 869.

In the forms of heart failure directly the result of overexertion there are several variations. Such acute attacks may be followed by complete recovery, but even with every precaution may develop into a chronic form. The commoner types may be grouped under four headings:

1. Young men accustomed to take violent exertion and engage in competitions frequently seek advice for palpitation, occasional giddiness or faintness, and an earlier onset of dyspnœa when undergoing exertion. The apex is usually well outside the nipple line, the impulse forcible and localized, the first sound is accentuated, loud and clear, and the second sound at the aortic area is accentuated; the pulse is large and strong, and the maximum blood pressure is increased.

2. Men of the ages of thirty-five to forty-five years who have for a number of years had laborious work as foundrymen, hammermen, etc., complain of fainting attacks or occasional vomiting and palpitation after exertion. They frequently have well-developed aortic regurgitation, and it is probable that in most cases the primary effect of the exertion has been atheroma of the aorta.

3. A third type occurs in young men of the working class. They complain of general ill-health and inability to do their ordinary work and perhaps some indigestion. They are sometimes mistaken for malingerers. On examination they are, as a rule, pale; the apex is in the nipple line, not easily localized and not forcible. There is marked epigastric pulsation. The area of dulness is increased to the right. The sounds are for the most part clear, but usually there is marked accentuation at the pulmonary aortic area. The pulse is not large or strong.

4. The fourth type is indistinguishable from a severe case of mitral regurgitation; the patient is bluish and dyspnœic; complains of great breathlessness on exertion and swelling of the legs.

The cause of the heart changes in *Graves' disease* is by no means sure. The capacity of the heart to do work is always more feeble in Graves' disease than in normal persons; any slight exertion causes breathlessness and an increase in the rapidity of the pulse. Serious cardiac failure in young subjects is by no means rare; it usually comes on after a period of steady loss in weight and, in fact, a fatal termination to the disease is usually the result of cardiac failure. In the early stages if the patient has been walking about there may be found a slightly displaced apex beat, a sudden impulse, a slight increase of dulness to the left, a slapping first sound at the apex, followed sometimes by a well-marked systolic murmur, an accentuated second sound over the pulmonary area at the base, and a pulse which is large in volume but poor in tension. Later, œdema, dyspnœa, and cyanosis appear with very little increase in the size of the heart. Postmortem, the cavities of the heart are not usually much dilated, the heart muscle is pale and not markedly increased in amount.

Barié[1] describes the reactions of dyspeptic states on the heart, stomach, and biliary tract. They result in a dilatation of the cavities of the right heart, accompanied sometimes by a secondary tricuspid insufficiency

[1] *Rev. de méd.*, 1883, vol. iii, p. 1.

with its clinical consequences. The form of attack is usually sudden and sets in with digestion. It is almost certainly nervous in its origin.

(f) The Action of Poisons.—The action of *alcohol* on the heart has been mentioned under Hypertrophy. Hypertrophy of the heart is the early stage; the later stage is heart failure with some special features. The heart is affected little by any other beverage than beer. The reason of this is not known; it is put down as being due to the alcohol, but this is not certain. The enormous quantity of fluid taken may be a factor and, again, many who suffer often lead arduous lives.

The cardiac affection usually comes on after the middle period of life has been passed; the patient finds that certain bodily exertions are impossible without a sensation of pressure or pain. Attacks of dyspnœa at night may trouble him. On examination the apex beat is outside its normal limits, somewhat feeble, and not easily localized. To percussion both ventricles of the heart are enlarged. The first sound is not pure at the apex, and the second over the aortic area is accentuated. The pulse is somewhat feeble, irregular, and easily quickened by exertion. Recovery from such symptoms with treatment is the rule, but usually the patient suffers from further attacks of heart failure, in one of which he dies. The symptoms are those of severe cardiac failure with considerable dilatation of the heart cavities. It is extremely difficult during the cardiac failure to exclude the possibility of renal disease.

The action of *tobacco* on the heart is usually seen from smoking strong cigars or strong tobacco in short pipes. Palpitation is the first sign and may be present in numbers of smokers without causing them any inconvenience. Attacks of palpitation are not uncommon and may come on without special cause in the night or after exercise, eating, or with excitement. Pain in the region of the heart is a frequent cause for seeking advice. Faintness on exertion is sometimes present. The pulse is usually small, quick, and often irregular. The size of the heart is, as a rule, not altered, but several competent observers have noted a definite increase.[1]

Poisoning with *tea* or *coffee* seldom causes alarming symptoms. Palpitation is the most frequent symptom, and occasionally apprehension, with pain in the chest.

Morbid Anatomy and Histology.—Pathological anatomy can seldom give an answer to the question whether a heart is insufficient to carry on its work. Many hearts that have not adequately performed their work during life hardly differ from normal hearts. But although we have not learned to recognize the conditions in the heart which give rise to cardiac failure, the anatomical effects in other organs are very striking—the cardiac liver and spleen afford us a sure means of determining death from heart failure. It must be remembered that the reserve power of the heart in a large number of persons is very small, and therefore a very insignificant lesion might produce a great upset in the circulatory balance if the recuperative power were small. Again, conditions of nutrition exercise a marked effect, for instance, old age, anemia, and tuberculosis may give rise to lesions recognizable with difficulty.

[1] See Krehl in *Nothnagel's Spec. Path. u. Therap.*, vol. xv, Band i, p. 262.

The hypertrophied heart is not as good as a normal heart. This is a clinical fact about which there can be no two opinions, and by a hypertrophied heart we mean one which gives definite signs of enlargement and therefore probably dilatation. Martius[1] has endeavored to explain this by saying that a definite amount of reserve power is at the disposal of the heart, and if more of this is used for ordinary purposes the less there will be for purposes beyond the ordinary. As it stands this can hardly be strictly true, for Hasenfeld and Romberg[2] have shown that a heart hypertrophied as the result of an artificial valvular lesion has practically the same reserve power as a normal heart. This, however, is not the case in valvular lesions in man, especially when there is some considerable hypertrophy, and it must then be supposed either that the limits of the normal working energy expended at rest are much overstepped or that in addition to the valvular defect there are others in the myocardium. In the commonest cause of valvular deficiency, namely, rheumatic fever, this is now highly probable. Aschoff and Tawara have described, in the muscle of such hearts, accumulations of large cells and giant cells, miliary and submiliary in size, in the connective tissue separating the muscle fibres or in the subendocardial tissue; these collections in the few cases examined have been frequently seen partly or wholly destroying the branches of the conducting system of fibres (Purkinje's fibres). They were constant in all the cases of true rheumatic fever examined and frequently also in those not of a certain rheumatic basis.

Much has been done in the way of a systematic search after the anatomical changes which underlie heart failure. The pioneers in this work have been Krehl and Romberg and their pupils of the Leipsic school. Many publications of great value have come from their researches, but it cannot yet be said that there is any unanimity in the opinions. The cases from which these results have been obtained are those dying from various forms of heart failure, especially valvular lesions, chronic hypertrophy from overindulgence in alcohol, renal disease, etc. Changes have been described in the nuclei, in the amount of pigment and fat, but neither these nor fragmentation of fibres, round-cell accumulations, or areas of fibrous tissue seem sufficient to throw any light on the problem.

Lesions of Special Muscle Bundles.—Albrecht, following the idea that heart insufficiency was due to lesions of particular bundles of muscle fibres, has attempted to show, on the basis of anatomical preparations, chiefly from the sheep's heart, that particular bundles of muscle fibres are affected, especially in the left ventricle, one connecting the posterior part of the ventricular septum with the posterior papillary muscle. Albrecht's conclusions have not been confirmed.

The Conducting System of Muscle Fibres.—Perhaps of greater significance than any publication of recent date, from the point of view of heart failure, is that of Tawara,[3] although the application of the facts there made clear has been done as yet in but a few instances. It is

[1] *Ergebnisse der Pathologie*, 1894.
[2] *Arch. f. exp. Path.*, 1897, vol. xxxix, p. 333.
[3] *Das Reitzleitungssystem des menschlichen Herzens*, Jena, 1906.

now a matter of common knowledge that a lesion of the bundle of His gives rise to the group of symptoms known as Stokes-Adams disease. Tawara, under the direction of Aschoff, following the methods of the Leipsic school, demonstrated that this bundle began in the neighborhood of the coronary sinus, in muscle fibres which were easily distinguishable from those of the auricular muscle itself. Shortly before entering the fibrous body of the heart the fibres interlace with one another, and here Tawara gives it the name of Knoten. It then pierces the fibrous body of the heart and appears on the top of the muscular septum of the ventricles, where it divides into right and left branches. These branches are subendocardial, the left spreading out into a fan-shaped area on the septal wall of the left ventricle, the right descending in a chink between two muscle columns on the septal wall of the right ventricle, giving off small branches to the neighboring muscle on its course. The ultimate ramifications of the bundle consists of Purkinje fibres, and are found on the surface of the muscle columns and as the false chordæ tendineæ, the whole being a system partly to convey muscular impulses from the auricle to the various parts of the ventricle, and partly in all probability to allow for a re-inception of the rhythm if the normal source should fail; the Purkinje fibres, being more primitive in structure, apparently retain in greater completeness their primitive functions, especially that of rhythmicity.

The right and left limbs of the bundle both convey fibres to the papillary muscles, the median papillary muscle of the right ventricle being supplied by a recurrent branch from the right limb.

More recently still, Keith and Flack have demonstrated that this system of fibres is of even greater significance. They have shown that in mammals, especially the mole, and in man there is a system of fibres at the origin of the great veins whose structure is easily distinguishable both from that of the venous muscle and that of the neighboring heart muscle. This muscular tissue is extremely like that in Tawara's system, and can be traced into the "Knoten" before named as well as in other directions. The muscular tissue at the roots of the veins sends branches to both auricles and the interauricular septum.

We have in this system, therefore, a complete skeleton of undifferentiated muscular tissue, added to which are the more differentiated parts of the heart. It serves the purpose of originating the impulse at the origin of the great veins and of conveying muscular impulses to the various parts of the heart. Aschoff and Tawara emphasize the importance of taking into account this system and its lesions in cases of heart failure. Albrecht certainly had the right notion in his attempt to find lesions of particular bundles of muscle tissue when explaining heart failure. Aschoff and Tawara have shown that in heart failure in acute rheumatic fever many of the lesions invade more especially the sites of the branches of this system. A thorough re-investigation of the subject of the anatomical changes in heart failure based on the present knowledge of this system is much to be desired.

Symptoms of Chronic Cardiac Failure.—(*a*) *Alimentary System.*—The most important are loss of appetite, indigestion, feelings of distension,

vomiting, pain in the abdomen, flatulence, meterorism, constipation, and hemorrhoids.

Two causes participate in producing these disturbances: First, the relations of the heart and stomach are such that any increase in the size of the stomach would interfere with the contractions of the heart, and at the same time even a moderate distension would interfere with the movements of the diaphragm; second, any failure of the right side of the heart produces an overfilling of the bloodvessels and consequent impairment of the organs of the abdomen. The actual condition of the organs in the latter state is one of œdema and venous congestion; catarrhal processes are present on all free surfaces—stomach, intestines, bile ducts, etc. Loss of appetite and indigestion are frequent signs of heart failure. They may be the first things brought to the patient's notice, and in the later stages, especially those in which the right side of the heart is at fault, they may be distressing, the patient preferring to be without food rather than submit himself to the discomfort attendant upon eating. With the inability of the stomach properly to digest or forward its contents the food undergoes fermentation with the production of gas; when this assumes a certain magnitude the distension impedes both respiration and cardiac action, and distress follows. Relief almost invariably follows copious eructations of the accumulated gas, but this not infrequently is difficult to attain, owing to deficient muscular power in the stomach itself and in the abdominal muscles.

Vomiting is not particularly common except under two conditions: it is met with frequently as a sign of heart failure in athletes after a hard race, and, secondly, it is a constant accompaniment of the later stages of any chronic form of heart failure; in the latter it is often a very bad prognostic sign. It is not possible at present to describe the mechanism by which this symptom arises; it seems to be an effect rather of left-sided than of right-sided heart failure, consequently we might attribute it to a deficiency in the blood supply to the medulla and a stimulation of the vomiting centre. This would receive some support from the analogy of the vomiting that occurs in shock. We must not lose sight, however, of the possibility of its also being due to a reflex stimulation of the vomiting centre by means of afferent impulses transmitted up the vagus fibres from the heart or stomach.

Pain in the abdomen may be dull and aching or sharp and lancinating. It may have its origin in the stomach from the condition set up there; it may be due to the distension of the liver and stretching of its capsule; a tender liver in heart disease is of frequent occurrence. On the other hand, it may be due to conditions in the intestine. It may be caused by an infarct in one of the mesenteric arteries. And last, it may be caused from angina, the pain being referred to the abdomen.

Any accumulation of gas in the intestine adds to the distress of the patient from the same reason as distension of the stomach; hence the necessity of special attention to the bowels. With the diminution in secretory activity there comes also a diminution in motility; hence the constipation, which is often troublesome. On the other hand, the œdema may be great and the irritation increased to such an extent that

a condition of diarrhœa is produced. Any condition of back pressure in the portal system acts unfavorably on those places where the portal and systemic system communicate; hemorrhoids, therefore, are frequent.

(*b*) *Cardiovascular System.*—Symptoms connected with this—the system that is at fault—are remarkably few. Palpitation is sometimes complained of, especially in those with large hearts. The patient is sometimes aware of a feeling of fulness in the chest, but this again may proceed from the abdominal organs. Pain referred actually to the cardiac region is infrequent; it is usual, of course, in inflammatory conditions of the pericardium, but here it is due undoubtedly to the stimulation of the nerves of the pericardium and not to any heart failure as such. Pain which is referred to other parts of the body, such as in the neck, down the arms, etc., is almost invariably anginoid.

(*c*) *Respiratory System.* — Under this heading come hyperpnœa, orthopnœa, and dyspnœa, attacks of dyspnœa—the so-called heart asthma—Cheyne-Stokes respiration, cough, hematemesis, and pain.

The various forms of breathlessness seem usually to be connected with a failure of the right side of the heart and are accompanied by some cyanosis. Haldane and Priestley[1] have demonstrated that the rate and depth of breathing is regulated by the amount of carbon dioxide which reaches the respiratory centre in a given time, or, in other words, if the tension of carbon dioxide in the blood remains the same, the circulation being unaltered, the rate and depth of respiration will not vary. If by an increase of the percentage of carbon dioxide in the air breathed in less is able to diffuse out from the blood, there is an immediate change in the amplitude of respiration which is seen to correspond accurately with the tension of carbon dioxide in the alveolar air. The tension of CO_2 in alveolar air rises during exercise owing to an increased amount being set free; consequently an increased ventilation takes place. From these experiments it is natural to conclude that the reason why hyperpnœa and dyspnœa are such common features in heart failure is because of a deficient elimination of carbon dioxide by the lungs, due primarily to a deficiency in the heart and a slowing of the circulation in the lungs.

It is well to limit the term *hyperpnœa* to an increase in the rate and depth of respirations, only applying the term *dyspnœa* to conditions in which there is distinct distress. *Orthopnœa* is that condition of hyperpnœa in which the patient assumes the upright position of the trunk, any attempt to lie down being immediately followed by an increase in respiratory distress. Its origin has been attributed to the mechanical conditions in the abdomen and neighborhood of the diaphragm. When orthopnœa is present the abdominal organs supplied by the portal vein are distended partly by blood and partly by œdema fluid. The hyperpnœa necessitates the greatest possible movement of the diaphragm and, if the contents of the abdomen are followed in a small degree to press against it, the force required in order to effect the necessary ventilation of the lungs must be greater. Orthopnœa, as we should expect, is confined to cardiac disease. According to Lazarus Barlow[2] the onset is

[1] *Journal of Physiology*, 1905, vol. xxxii, p. 225.
[2] *General Pathology*, London, 2d ed., p. 685.

usually sudden; it is complete from the first; the condition rarely recedes and frequently advances. The angle assumed by the patient is the nearer a right angle the greater the distress. At postmortem there is a dilatation of the right ventricle in 80 per cent. of the cases.

Another factor must be taken into account in considering dyspnœa in cardiac disease. V. Basch supposes that, other things being the same, the extensibility of the lungs becomes less in proportion as the pressure of the blood in the capillaries of the lungs becomes greater, that with greater filling of the lung capillaries the lungs become stiffer. This condition he calls "Lungenstarrheit." It hinders both the expansion of the lungs on inspiration and their contraction on expiration. With the same overfilling of the lungs with blood, owing to a straightening out of the capillaries in the walls of the alveoli, there is an enlargement of the cavity of the alveolus which gives rise to an enlargement of the whole lung (Lungenschwellung). Both of these conditions would act so as to require a greater expenditure of muscular force to effect the normal ventilation of the lungs. Although the general truth of the proposition is admitted and has been demonstrated by experiment, there is as yet not evidence enough to assert that under the conditions of congestion of the lungs occurring in heart disease it is present to a degree capable of offering a great hindrance to respiration.

In the sudden attacks of dyspnœa known as "cardiac asthma" we must look probably to other causes than those just mentioned. The attacks usually come on at night at the same time as some of the paroxysmal neuroses. The onset is sudden, the distress great, and the face is usually pale. These features suggest a nervous element which, in this particular sense, is wanting in the ordinary cardiac dyspnœa. The pulse is rapid, soft, and irregular in force and frequency. This causes an increase of pressure in the pulmonary vessels. François-Franck found that irritation of the heart or aorta produced reflex respiratory phenomena, such as spasm of the larynx and bronchi, which was intensified by the coexistence of a valvular lesion. Cardiac asthma may be the first sign of heart failure to the patient; it may come on after excitement, a meal, the slightest extra exertion, or without any adequate reason. Krehl notes the frequency of cardiac asthma in arteriosclerosis, coronary artery disease, and nephritis, and from the features of the attack and the association with cardiac disease supposes that it is due to temporary weakness of the left ventricle and some increase of pressure and loss of velocity of the blood in the lungs.

Cough in cardiac disease occurs first in acute cardiac failure under the same conditions as vomiting in overexertion: in fact, coughing is frequently suggestive of a milder form of cardiac failure, vomiting appearing later and in the severer forms. It may occur in chronic cases probably from failure of the medullary circulation. But by far the most common cause of its appearance is the reflex stimulation of afferent nerves to the respiratory centre in the medulla. Changes in the pleura and accumulation of fluid may produce the same.

Hemoptysis is a very common symptom in cardiac failure, especially from disease which affects the mitral valve. It may vary from a sudden

profuse hemorrhage, such as is seen in cases of mitral stenosis, to slight streaks of blood in the sputum. When it occurs early in the course of a mitral stenosis it may be looked upon as compensatory and a relief to an overfilled lesser circulation. In the later stages of mitral failure small hemorrhages are frequent. From postmortem records we know that in these cases there is often marked sclerosis of the pulmonary vessels; many of these probably have weakened spots and, with the continuance of the increased pressure, give way, causing hemorrhage into the lungs and bronchi; the former probably are the cause of the infarcts so frequently seen in the lungs, and the latter produce a tinge of blood in the expectoration without the clinical signs of an infarct.

(*d*) *Central Nervous System.*—Apart from the symptoms due to gross brain disease, such as embolism, thrombosis, hemorrhage, etc., there are many symptoms whose origin is not clear.

Increase of brain activity, sleeplessness, and mania are not infrequent. Two factors must be thought of: first, lack of nourishment from insufficient filling of capillaries, and, secondly, uremia. Of uremia in cardiac disease we know little; it may come on from continual disturbance of the kidney cells from insufficient arterial blood supply, from pressure on the kidneys due to ascites, and possibly from other conditions.

Unconsciousness in heart disease comes on when there is a marked deficiency in the amount of blood that reaches the brain, and in those in whom the deficiency remains death results. It is not always possible to attribute fainting attacks in normal persons to momentary deficiency in heart action; many such may be due to sudden loss of tonus in the splanchnic area, but since we know that a sudden stoppage of the heart can be produced by the action of the vagus nerve it is right to assume that some attacks of fainting are due to lack of proper blood supply to the brain. The same objection cannot hold when the heart itself is at fault. Sudden fainting in fatty degeneration of the heart and in coronary artery disease with a fatal termination is well known. One of the common symptoms of aortic disease, often the one which first comes to the notice of the patient, is fainting. In aortic disease, if a proper supply of blood is to be given to the brain, the minimum blood pressure must be kept above a certain limit. The blood pressure in aortic disease varies between very wide limits; the maximum is frequently great, 150 to 160 mm., and the minimum may be 80 to 90 mm. To prevent lack of cerebral blood it is necessary that this minimum should not be unduly lowered. But the pulse intermits or has an extrasystole and a longer interval between two normal beats, the outflow from the aorta into the heart is not adequately checked during the period of the abortive beat and the system becomes abnormally empty.

Stupor and drowsiness are seldom seen except toward the end of life or in very severe cardiac disturbance. Probably the same cause acts here as in unconsciousness, the failure of the left ventricle properly to fill the arterial system; but from its presence in cases in which the right side of the heart is mainly at fault, with great cyanosis and œdema, we must take into account the possibility of its being due to a chronic poisoning by carbon dioxide with which the capillary blood is overcharged.

Epileptiform Convulsions.—The recent attention which has been given to the study of Stokes-Adams disease leaves no doubt that cerebral anemia can give rise to unconsciousness, and also to convulsions. In Stokes-Adams disease there are differences in the onset of the convulsions, but usually, as in the patient described by Webster,[1] in whom the heart would intermit for periods of ten to twenty seconds, the first warning was pallor of the face coincident with a disappearance of the pulse at the wrist; after some fifteen seconds of absence of the pulse spasmodic twitchings of the muscles of the face were observed; as the period increased the spasmodic movements spread first to the muscles of the neck and ultimately to the arms, trunk, and leg. With the more severe attacks there was concomitant squint or conjugate deviation of both eyes to one or other side. The pupils were widely dilated, respiration was noisy, and froth appeared at the mouth. Unconsciousness during the greater part of the period was complete, and with the return of consciousness flushing of the face occurred with the appearance of the pulse at the wrist.

(*e*) *Integumentary System.*—Cyanosis is due to an overabundance of reduced hemoglobin in the vessels of the skin. It is not necessarily associated with heart disease. Many normal persons continually have blue hands, ears, and cheeks; in these cases local conditions of the circulation are the cause, for it seldom affects the lips. Again, a cyanotic tint can be seen during cold weather in the faces of persons who are much exposed; in them it is due to capillary dilatation and slowing of the circulation.

Œdema.—The œdema of cardiac disease is easily recognized; it occurs first in those parts of the body which are most dependent, in the ankles if the patient is out of bed, in the buttocks or calves if the patient is in bed. The skin looks thin and more transparent; if the œdema is great it may be smooth and shiny. Most patients complain of some pain on pressure over œdematous parts. If the œdema has lasted for a month or two or if the patient has been walking about, the œdema becomes very hard and considerable pressure is necessary to cause pitting.

Richard Lower, in 1680, first showed the connection of increased pressure in the veins with the production of œdema; he found that œdema of both lower limbs came on as the result of tying the inferior vena cava; on this experiment he explained the pressure of œdema in cardiac disease. There are three possibilities open according to modern views for an explanation of cardiac œdema whose immediate cause is an overfilling of the veins; it may be due to an increase of pressure and filtration of œdema fluid from the vessels from which transudation normally takes place, namely, in the capillaries; it may be due to an alteration in the permeability of the vessel wall, or it may be due to an increased secretory activity on the part of the cells of the capillary walls. Increase of pressure in the capillaries, although it undoubtedly occurs in cardiac disease, is not the immediate factor in its production, for cutting the vasomotor nerves to a limb and stimulating the spinal cord to produce a

[1] *Glasgow Hospital Reports*, 1900, vol. iii, p. 413.

dilatation of the small arteries and an increase in aortic blood pressure respectively does not result in any œdema of the limb. Again, if the pressure was the immediate cause of the exudation, tying of the veins should in a short time be followed by an increased lymph flow and the appearance of œdema, but these only appear several hours after the increase of pressure.

The factor of importance is the lack of proper nutrition, both liquid and gaseous, to the tissues as well as an interference with the removal of waste products. If hemostasis is produced in a limb for an hour, by tying a ligature tightly around it, the specific gravity of the venous blood and of the plasma rises and the lymph flow falls; after the removal of the ligature a small increase of venous pressure easily gives rise to œdema. The tendency to œdema is great if the limb has been rendered anemic for an hour by means of an Esmarch bandage. These experiments show the importance of the tissues in the formation of cardiac œdema as opposed to the view first enunciated by Ludwig, that it is due exclusively to the conditions of pressure in the capillaries. Whether the œdema of cardiac disease is a filtrate or a secretion cannot as yet be decided.

(*f*) *Renal Conditions in Cardiac Disease.*—The features of the urine in cardiac disease are as follows: A great lessening in the total amount excreted, even to a half or less than the amount excreted before on the same intake of fluid; the color becomes darker, with that the concentration is greater and the specific gravity rises; the reaction is usually strongly acid; deposits after standing are very common. The urea reaches about 5 per cent. in the concentrated urine. The uric acid is often in relatively greater amount than under normal circumstances. It has been shown[1] that leucin and tyrosin can be found in the urine of cases in which the liver is enlarged from cardiac disease. The inorganic salts are found to vary considerably in amount. A small amount of albumin is usually found (0.05 to 0.2 per cent. by Esbach's method of estimation). The sediment contains in a large number of cases white-blood cells, an occasional red cell, and a few casts, most frequently hyaline, but sometimes granular and even cellular ones are found.

These changes are found only in those cases in which the function of the right side of the heart is at fault, accompanied by congestion in the venous system. It has been proved by Dreser that even when the dilutest urine is secreted the cells of the kidney do an appreciable amount of work in transferring the waste substances in the blood into the tubules of the kidneys, so that with urine of ordinary concentration considerable work has been expended by the kidney. To do this work properly the kidney must be supplied with its normal amount of arterial blood, for if not, the cells form large quantities of sarcolactic acid and undergo changes which are the beginnings of necrosis. The large amount of sarcolactic acid will account for the constant and well-marked acidity of the urine in cardiac patients; the necrotic changes in the cells of the tubules will account for the increase of uric acid and the presence of albumin; it is not so easy to account for the concentration of the urine. It might have been thought that as the kidney partakes in the tendency

[1] Dixon Mann, *Quarterly Journal of Medicine*, 1907, p. 25.

to become œdematous the urine would have been more diluted, but normally the concentration of the urine seems to be determined on the one hand by conditions of the blood and on the other hand by the conditions of the blood supply. If the sweat glands are excreting vigorously there is in all probability a tendency for the blood to become more concentrated; the urine now contains less water and rises in specific gravity. If, on the other hand, the peripheral arteries are constricted and the blood pressure rises in the internal organs of the body, the kidneys, as, for instance, under the influence of cold, excrete a large amount of dilute urine. We must probably look to the constant loss of the watery constituents of the blood in the form of œdema fluid elsewhere as the reason for the high specific gravity of the urine, for it has been proved that the blood in conditions with œdema is more concentrated. Further, the formation of œdema fluid takes place as a transudate from the veins rather than from the capillaries nearest the arteries which are more concerned in the secretion of urine.

The Blood Pressure in Relation to Cardiac Failure. — It was hoped that some indication of the state of the heart was to be found in the records of blood pressure. Such a hope has hardly been justified. As Hensen[1] points out, the variations in the blood pressure of normal persons differ greatly, and in heart failure, especially mitral disease, the irregularity of the heart is such that definite figures cannot be obtained. In most of the published records of blood pressure the maximum is the only one recorded, but when one considers that in a case of irregular heart from mitral failure the summits of the pulse waves on a tracing vary considerably it is obvious that no constant value can be obtained.

It is different, however, if we take the maximum record obtainable. If one is dealing with young adults without evidence of renal disease an estimate of their maximum blood pressure at something less than 125 mm. of mercury is probably within the limits apart from psychical or other disturbances. If, then, taking the highest maximum blood pressure we find a value of 140 it is clearly abnormal. Katzenstein[2] has called attention to the fact that in early heart failure, such as can be seen in chlorotic girls, the blood pressure is higher than is expected and may be high when the pulse at the wrist is small and feeble. We are probably justified in taking Katzenstein's explanation that it is an evidence of a compensatory mechanism, probably a peripheral arterial constriction directed toward an adequate upkeep of average blood pressure.

The difficulty of determining by clinical methods the extent to which any given heart can do extra work is a serious deficiency in the matter of forming an opinion for the future guidance of the patient. Some hearts, for instance, although hypertrophied, will show no signs of failure for many years; others, again, even though the hypertrophy may only be small and not of long duration, may often show signs of heart failure, sometimes acute in its onset.

Treatment.—This is discussed in the section on Valvular Diseases.

[1] *Deutsch. Arch. f. klin. Med.*, 1900, vol. lxvii, p. 512.
[2] *Hypertrophie u. Dilatation*, München.

CHAPTER VIII.

DISEASES OF THE VALVES OF THE HEART.

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AND

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INTRODUCTION.

General Etiology and Morbid Anatomy.—Acquired valvular defects are the sequence of acute endocarditis or the result of a primary fibrosis. In both cases the effect is the same—a deformity, puckering, and adhesion of the valves, leading to insufficiency or stenosis, or to both combined. Chronic disease of the valves of the heart, then, is a question almost exclusively of valvular fibrosis.

In about 50 per cent. of all the cases this sclerosis is a sequence of acute endocarditis. Among 670 cases of chronic heart disease at the Leipsic clinic, 58.5 per cent. followed acute rheumatism (Romberg). Other acute diseases of childhood are responsible for a certain number of cases, while in a not inconsiderable proportion, particularly of mitral cases, no etiological factor can be determined. In the other great group there is a primary degenerative change in the valve of very much the same nature as arteriosclerosis. There is a senile form which follows the ordinary wear and tear of life. All conditions which keep up permanent high tension lead to thickening and puckering of the aortic and mitral segments; while certain poisons, alcohol, tobacco, and syphilis, may cause primary sclerotic changes in the valves, just as they do in the arteries. The morbid anatomy of chronic valvular fibrosis is very characteristic. In the early stages the edges of the valves are a little thickened and may present nodular bodies, the remnants of organized vegetations. In the aortic segments the corpora Arantii enlarge, the edges thicken, the substance of the valve loses its translucency, and along the line of attachment to the aorta there is opaque sclerosis. In the auriculoventricular valves these early changes are seen just within the margin, and here it is not uncommon to find swellings of a grayish red, somewhat infiltrated appearance, almost identical with the similar structures on the intima of the aorta in arteriosclerosis. Even early there may be seen yellow or opaque white subintimal fatty degenerated areas. As the sclerotic changes increase, the fibrous tissue contracts and produces thickening and deformity of the segment, the edges of which become round, curled, and incapable of that delicate apposition necessary for perfect closure. A sigmoid valve, for instance, may be narrowed one-fourth or even one-third across its face, the most extreme grade of

insufficiency being induced without any special deformity and without any narrowing of the arterial orifice. In the auriculoventricular segments a simple process of thickening and curling of the edges of the valves, inducing a failure to close without forming any obstruction to the normal course of the blood flow, is less common. Still, we meet with instances at the mitral orifice, particularly in children, in which the edges of the valves are curled and thickened, so that there is extreme insufficiency without any material narrowing of the orifice. More frequently, as the disease advances, the chordæ tendineæ become thickened, first at the valvular ends and then along their course. The edges of the valves at their angles are gradually drawn together and there is a narrowing of the orifice, leading in the aorta to more or less stenosis, and in the left auriculoventricular orifice—the two sites most frequently involved—to constriction.

Finally, in the sclerotic and necrotic tissues, lime salts are deposited and may even reach the deeper structures of the fibrous rings, so that the entire valve becomes a dense calcareous mass with scarcely a remnant of normal tissue. The chordæ tendineæ may gradually become shortened, greatly thickened, and in extreme cases the papillary muscles are implanted directly upon the sclerotic and deformed valve. The apices of the papillary muscles usually show marked fibroid change

Incidence of Involvement of the Valves.—In the collected statistics of Parrot the mitral orifice was involved in 621 cases, the aortic in 380, the tricuspid in 46, and the pulmonary in 11.

Mortality.—The death rate in England and Wales from circulatory disease is 1.66 per 1000. In 1905, 242,276 males, 265,454 females died of diseases of the circulatory system. When one considers that a very large proportion of these cases have their origin in rheumatic fever, we see what an important rôle this disease plays among the acute infections. The larger number of females is probably owing to the fact that rheumatism and chorea are more common among them.

Age Incidence.—Fully one-half of the cases of valvular disease of the heart occur in young persons. Up to the fifth year children are not very liable to valvular disease, but from the fifth to the tenth a great many cases of chorea and the milder types of rheumatism lay the foundation for subsequent sclerotic changes. Doubtless, many cases of mitral disease owe their origin to the slight valvulitis arising in the course of a tonsillitis. Between the tenth and fifteenth years there is an ever-increasing liability. From this time, onward, the endocarditic valve lesions diminish. During the adult period, from the twentieth to the thirtieth year, the maximum number of cases of cardiac breakdown occur —37.16 per cent. in Romberg's Leipsic statistics. In the fourth decade a considerable number of the endocarditis cases drop out and the special sclerotic forms begin to appear, more particularly the syphilitic and those associated with the toxic types of sclerosis. Through the fifth, sixth, and seventh decades there is a progressively diminishing incidence. The figures in Romberg's statistics were for the fifth decade, 12.69 per cent.; for the sixth, 9.10 per cent.; for the seventh, 4.33 per cent.; and for the eighth, 1.05 per cent.

Effects of the Valve Lesions.—The general influence on the work of the heart may be briefly stated as follows: The sclerosis induces insufficiency or stenosis, separately or in combination. Narrowing retards the normal outflow; insufficiency permits a certain reflux of blood, with the effect of dilatation of the chamber behind the affected valve. In the former case the chamber has a difficulty in expelling its contents through the narrow orifice; in the latter the chamber is overfilled by blood flowing into it from an improper source, as, for instance, in mitral insufficiency, when the left auricle receives a double current from the pulmonary veins and from the left ventricle.

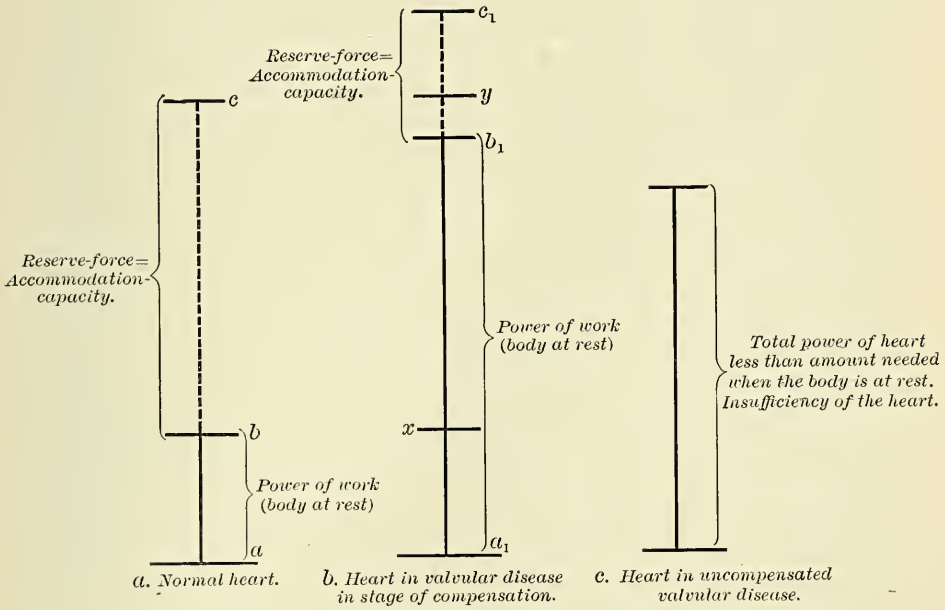
The heart is fully prepared to meet the ordinary grades of dilatation which constantly arise during the extra calls of exertion, when, as in the course of a fever, its muscle has been enfeebled. Supposing as in valvular disease, the dilatation of a cavity is permanent, then the constant extra stimulation of the heart required to keep the circulation properly maintained calls forth hypertrophy (see article on Hypertrophy) to combat this extra constant demand upon the heart's resources. When the inception of valvular disease is slow, as from sclerotic changes, the increased activity of heart muscle calling forth a gradual hypertrophy is able to avert any lack of compensation until the valvular deficiency oversteps the limits which increased activity and hypertrophy can oppose. On the other hand, if the valvular defect occurs rapidly, then compensation is disturbed in proportion to the magnitude of the deficiency and its rate of onset, and the heart remains uncompensated until hypertrophy has time to develop. To appreciate its nature the process may be graphically shown in the accompanying diagrams, in which the perpendicular lines represent the power of the work of the heart. While the muscle in the healthy heart (Fig. 11 *a*) has at its disposal the maximal force, *a c*, it carries on its work under ordinary circumstances (when the body is at rest) with the force *a b;* and *b c* is the reserve by means of which the heart accommodates itself to greater exertion.

With a gross valvular lesion the force needed to do the ordinary work (at rest) becomes very much increased (Fig. 11 *b*). But in spite of this enormous call for force, insufficiency of the heart muscle does not necessarily result, for the working force required is still within the limits of the maximal power of the heart, $a_1\ b_1$ being less than *a c*. The muscle accommodates itself to the new conditions by making its reserve mobile. But this condition could not be permanently maintained, for there is nothing left for emergencies but the small reserve force $b_1\ y$. Even when at rest, the heart would be using continuously almost its maximal power. Any slight exertion requiring more extra force than that represented by the small value $b_1\ y$ (say the effort required in walking or in going up stairs) would bring the heart to the limit of its working power and palpitation and dyspnœa would appear. The increased exertion leads now to the putting on of yet more muscle, enabling the heart the better to meet the added calls on its strength, and with this the extreme limit of cardiac action is raised, and instead of this being at *y*, it now reaches c_1, provided there is no interference with the nutrition of the heart muscle.

To what extent the various degress of valvular insufficiency call forth

an increase in reserve power is difficult to decide. It is probable that with a slight lesion the limit at first is not beyond what it would be in a similar normal heart under the same conditions, but when the requirements of the heart, with the body at rest, increase so as to approach the limit of the reserve power, we may infer that the total cardiac capacity is increased in proportion because, unless absolute rest of the body, and probably also of mind, is maintained, any movement and any excitement increase the work of the heart and widen the upper limit of cardiac capacity.

FIG. 11



(After Martius.)

The property of the heart whereby at times greater work can be sustained than when the organ is at rest has an important bearing on the course and the treatment of organic lesions. *Per se*, a valvular lesion if slight may affect but little, if at all, the limits to which cardiac action can be pushed; in other words, a person with a well-marked valvular lesion sometimes endures, without any outward symptoms of excessive distress, the most arduous trials of endurance. This is in agreement with the results of Hasenfeld's experiments, which demonstrate that the limits of cardiac endurance in rabbits with lesions of the aortic valves are hardly if at all lessened as compared with a normal rabbit. But it must not be supposed that a person with valvular disease can undergo with impunity as arduous, continuous exercise as a person with a normal heart. Because, first, the total work required of such a heart at the height of the exertion is far above that asked of the normal heart under similar circumstances; secondly, valvular lesions in man, especially those from rheumatism, hardly ever leave the muscle in the same state

as before, so that less work can be got out of it and the inevitable dilatation leads to a yet further increase in the heart's requirements at rest.

The Reserve, a function of cardiac muscle alone, is well marked in youth and increased up to adult age and thereafter diminishes; it is also affected by any interference with cardiac muscle, such as infections, intoxications, malnutrition. In all valvular lesions these rest and reserve capacities should receive consideration. In the early periods, the heart's work should be well within the rest limit, so as to throw as little strain as possible on the affected valves and allow healing to take place. When this is accomplished, exercise should be so regulated that the reserve is not called upon too suddenly or too freely, while at the same time the limits of cardiac response are gradually widened. If we condemn a person with valvular disease to live always at or about his rest limits, we may tend to retard the growth of his cardiac reserve. On the other hand, it would invite an attack of cardiac failure to ask him to do an arduous piece of work, or if he had to undergo a serious infection. In valvular disease, although an increased amount of work is demanded of the heart, with the body at rest, the full reserve should, if possible—the part *b* to *c* in the diagram—be developed and maintained in young persons, in whom normally these limits are easily extended by daily exercise. There is no reason why a lad with valvular disease should not in a modified degree undergo the same training as a healthy one. In persons who have arrived at an age when cardiac muscle begins to degenerate, the greatest care must be taken. In compensated lesions, exercise of the heart, *i. e.*, work over and above the rest limit, is usually beneficial, but a thorough survey of the patient's cardiac condition should be made from time to time, and the effects of this exercise carefully studied. A heart which undergoes increased exertion gets an hypertrophy of work (see section on Hypertrophy), enlarging in all its parts and the weight increasing. But although the cavities enlarge somewhat, they do so probably in some (as yet unknown) proportion to the increase in the bulk of the muscle. On the other hand, hypertrophy that follows a valvular deficiency results from the enlargement of a cavity beyond the normal limits to allow of accommodation. The compensation by which an extra amount of blood is forwarded is the expression of the amount of blood in the cavity. Without such hypertrophy the circulation would not be adequately maintained even at rest. The hypertrophy of valvular disease is to be compared accurately with that from overexertion, due in both to a dilatation of one or more cardiac cavities. If a valvular deficiency could be made good, we should expect, as in the treatment of hearts overstrained as the result of exercise, a return of the organ to normal bulk, for no other reason than that the cavity has again resumed its normal, or nearly its normal, size at the beginning of systole.

No doubt the capacity of the heart to hypertrophy in valvular disease is limited by the extent to which the hypertrophy of work can be attained, and such a result in an aged person is not so easily compensated as in a younger one, and the greater the insufficiency the less chance there is to increase the limits of cardiac reserve by hypertrophy.

Turning now to the disturbance of *compensation*, it is to be borne in mind that any heart, normal or diseased, may become insufficient whenever the call for work exceeds the maximal capacity. The liability to such disturbance will depend, above all, upon the accommodation limits of the heart, the less the width of the latter, the easier will it be to go beyond the heart's efficiency. A comparison of diagrams *a* and *b* (Fig. 11) will immediately make it clear that the heart in valvular disease will much earlier become insufficient than the heart of a healthy person. If the heart muscle be compelled to do maximal or nearly maximal work for a long time it becomes exhausted; or, to be more specific, the mechanism by which extra work is called forth from the heart, namely, stimulation of the heart muscle by stretching, and reflexly by the sympathetic nerves from underfilling of the peripheral vessels, fails to act further; the muscle now becomes more stretched, the blood supply is interfered with, and the circulation becomes insufficient at that point. In valvular disease, on account of its small amount of reserve force, the heart has to do maximal or nearly maximal work far more frequently than does the normal heart. By stretching of its walls or interference from myocardial degeneration or disease, its power falls below the amount necessary to carry on the work of the heart when the body is at rest, or it may cease to be sufficient even for this. The reserve force gained through the compensatory process may be entirely lost (Fig. 11 *c*). On the other hand, the insufficiency of the valve at fault may make demands on the heart up to such a point that it approaches and oversteps the upper limit of cardiac accommodation. In the first case, if the loss of reserve force is only temporary, *i. e.*, if the demands on the heart are lessened by rest, or if the muscle can be allowed to recover, the condition is spoken of as a "disturbance of compensation." The term decompensation or "loss of compensation" is reserved for the condition in which the disturbance is permanent.

INSUFFICIENCY OF THE AORTIC VALVES.

Etiology and Morbid Anatomy.—The sigmoid valves guarding the aortic orifice become insufficient under many different conditions, which are important to recognize, particularly as they have a bearing on prognosis.

The frequency of the disease varies in different localities and in different hospitals. Where the patients are from the working classes in large manufacturing centres, and in seaport towns where syphilis prevails, the number of cases is very large. On the other hand, in hospitals with a large proportion of children, aortic insufficiency is relatively rare.

One of the most carefully compiled sets of figures is that from the Edinburgh Infirmary.[1] Of 2368 cases with cardiac lesions, valvular disease occurred in 80.8 per cent. (1914 cases); 7.3 per cent. of these 1914 cases were aortic insufficiency alone and 17.6 per cent. aortic insufficiency with mitral disease. Barié gives the proportion at 37 per

[1] Gillespie, *Edinburgh Hospital Reports*, 1898, vol. v, p. 31.

cent. It is the most common form of aortic valvular disease. The ratio between stenosis and insufficiency is very variously given, owing to the fact that the recognition of the former is not nearly so easy, as in many instances the diagnosis of stenosis has rested simply on the presence of a basic systolic murmur. But in hospital practice the senior author would say that aortic insufficiency was ten times as numerous. In his private consultation work, in fifteen years the proportion of insufficiency to stenosis cases was 7 to 1.

Age.—It is a comparatively rare affection in childhood, and is most common in men in the fifth and sixth decades. The form following endocarditis occurs at an earlier age, and is met with in children and young adults. A luetic form is met with in comparatively young men. The arteriosclerotic occurs most frequently between the ages of forty and sixty.

At least five groups of cases may be distinguished according to their mode of origin.

1. **Endocarditic.**—The acute infections with which endocarditis is associated, attack the aortic and mitral valves with varying frequency. Rheumatic fever and chorea have a special predilection for the mitral segments. The ordinary septic types attack aortic and mitral valves alike. The severe pneumococcic and gonococcic forms are perhaps seen more frequently on the aortic segments. The ordinary endocarditis of rheumatic fever in children, even when it attacks the aortic valves, does not, as a rule, leave them incompetent. The chaplets of little vegetations may disappear without leaving much, if any, damage. In other cases the edge of one or of two valves is thickened, slightly curled, so that they do not come into close apposition during diastole, and in consequence there is a slight leak. In yet a third group of cases endocarditis has been more severe. The substance of the valve itself has been involved. The segments become adherent, calcification takes place in the hyaline and necrotic tissue, so that the aortic orifice is itself narrowed and there is a combination of stenosis and insufficiency. Sometimes, as a result of the endocarditis, one valve only is affected and a rigid calcified spur remains which prevents the proper closure of the valve. The distinguishing features of the endocarditis group are: the earlier age, the absence of involvement of the root of the aorta so that the coronary arteries are unimpaired, and the greater frequency of the combination of narrowing with stenosis, particularly in young persons. There is a very acute endocarditic-aortic insufficiency coming on in the course of a severe rheumatic endocarditis or in the ulcerative forms in septicemia, pneumonia, and gonorrhœa. Within a week, even within three or four days, the signs of aortic insufficiency may be well marked. In the rheumatic cases recovery may take place, but in the septic forms a malignant endocarditis is apt to develop.

2. **Arteriosclerotic.**—In this, by far the most important form, the insufficiency is part of a widespread arteriosclerosis or of a lesion limited to the root of the aorta. The segments really behave as portions of the aorta, and are involved with it in the degenerative changes. After forty, the aortic segments always show slight signs of wear and tear, and in

hard drinkers and hard workers with arteriosclerosis the segments become involved also. The exceedingly delicate texture is lost, the edges curl, and the segments thicken, become foreshortened and so unable to come into close apposition during diastole. So slight is the alteration in some cases that the valves look almost normal, or there may be shortening of only one segment. The surface of the valves may be perfectly smooth, without calcifications or adhesions between the segments, so that there is no narrowing of the orifice. There has been in the valve a simple progressive sclerosis. With this a varying degree of involvement of the arch of the aorta and of the vessels generally is associated; sometimes the arch is in an advanced state of endarteritis deformans, greatly dilated, and even aneurismal. But in other instances the valves themselves show relatively more disease than the aorta. The orifices of the coronary arteries are involved, usually narrowed by the endarteritis, or the branches of the vessels themselves may be diseased. This is the common type met with in hardworking men between forty and sixty, in whom there has been no history of rheumatism but the common factors responsible for arteriosclerosis.

Two other varieties may be placed in this category. The *luetic* form of aortic insufficiency occurs in young men usually within two or three years from the date of infection. It is associated with a syphilitic mesarteritis of the root of the aorta, which may directly implicate the adjoining segments. It comes on with severe pain, frequently anginal in character. The insufficiency gradually develops under observation. Sudden death may occur from the involvement of the coronary arteries. In other instances, with appropriate treatment, the condition improves and the case finally settles into one of chronic aortic insufficiency. A parasyphilitic variety is seen in connection with locomotor ataxia. This is probably a degenerative form due to the slow action of toxins, but it may occur in the tabes in comparatively young men who have no widespread arterial degeneration. A *senile* type of aortic insufficiency is not very infrequent. Met with in men over seventy it is due to a gradual thickening, calcification, and adhesion between the segments, so that there is narrowing of the orifice and slight permanent insufficiency.

3. **Relative Insufficiency.**—Corrigan recognized this in his original paper, and stated that without any organic lesion of the segments, insufficiency might be caused by dilatation of the aortic orifice. Discussion has taken place as to the existence of this form. While rare, there can be no question of its occurrence. Experimentally it has been produced by section of certain muscular strands. Beneke showed that the circumference of the aortic orifice and the aorta just above it increase slightly as age advances, no doubt owing to loss of the elasticity. The cases of this variety have marked dilatation of the aorta, often with exteme endarteritis deformans, and the sigmoid valves a little thickened at the corpora Arantii and along the free border, but without reduction of the closure surface of the valve.

4. **Rupture of the Valve.**—This accident rarely happens to a healthy valve, but it has been quite frequently met with in disease following the strain of a sudden exertion upon segments already diseased or the seat

of endocarditis. Still more often it has followed a trauma, a kick from a horse on the chest, or a fall. One or two valves may be involved. It is more frequent in the aortic than in the other valves. Of 72 observations collected by Dreyfus, 46 were of the aortic segments.

5. **Congenital.**—A considerable number of cases are due to congenital malformation of the segments, resulting in a fusion of two of the cusps, and almost invariably those behind which the coronary arteries are given off. By no means an infrequent condition; of 17 cases, all of which presented sclerotic changes, the majority had had during life the clinical features of chronic heart disease. The cases are not always congenital, and the mode of production has been discussed by Dr. Maude Abbott in the section on Congenital Diseases of the Heart.

Pathological Physiology.—The prevalent views of the condition of the heart and bloodvessels in aortic regurgitation require some modification. It is commonly held that with a defect in the valves a large amount of blood flows back into the ventricle from the aorta, and that the distension thus produced in diastole has a greater tendency than normal to distend the chamber. But Stewart[1] showed that the quantity regurgitated, except in very marked degrees of the condition, is not more than a small fraction of the total amount of blood in the ventricle. The effect of the regurgitation is to counterbalance the negative pressure present in the chamber immediately after systole and to put a positive pressure in the ventricle in all periods of diastole. The effect of this positive pressure is to cause an increased tone of the ventricular muscle, as can be shown by comparing the volume curves of the heart in the normal animal and after the production of regurgitation. The probable explanation of this is that the cardiac muscle in aortic regurgitation is "overloaded," for Stewart determined that, as in an overloaded frog's muscle, the summit of the curve occurs after that of the normal. He showed, moreover, that the collapsing pulse is not due to regurgitation into the left ventricle, but to a reflex dilatation of the peripheral arterioles from stimulation of the ventricular wall by the increased pressure. In some of his experiments, when the operation failed to produce the lesion of the aortic valve, nevertheless, as a result of touching the ventricular wall, the typical features of aortic regurgitation were evident in the records. Stewart explained this reflex as the normal means of preventing the effects of undue pressure in the cavities of the heart. The collapsing pulse in experimental animals is changed to one that is more normal by increasing the peripheral constriction, as, for instance, by compressing the abdominal aorta or by injecting adrenalin; and this is confirmed by finding that compression of the vascular area peripheral to the radial artery in a case of pure aortic regurgitation produces the same result. This fact, the low peripheral resistance in aortic regurgitation, is probably the reason for the frequent presence of capillary and sometimes even venous pulsation.

The *Corrigan pulse* is more marked when the radial artery is felt with the arm held vertical. This is probably not due to the accentuation of

[1] *Archives of Internal Medicine*, Chicago, 1908, vol. i, No. 1.

regurgitation, but to the diminished venous pressure and consequent greater capillary flow; for if in this position the veins be constricted, the collapsing pulse tends to disappear. A slowing of the heart beat of itself is probably not harmful if tonus is well maintained, because the volume curves in experimental animals show no greater filling of the ventricle during vagus stimulation than before. The harmful effect of digitalis in certain cases of aortic regurgitation is due not so much to the retardation of the rate of the heart, as to the peripheral constriction opposing the vasodilatation which is calculated to relieve the heart.

The blood pressure in aortic regurgitation shows very constant features in experimental animals. The systolic blood pressure remains the same within very narrow limits, the diastolic is invariably lessened, and therefore the pulse pressure, or the difference between them, is increased. This is not so in all cases in man. Two varieties have been distinguished: first the rheumatic in which both maximum and minimum pressures are lowered and, secondly, the arteriosclerotic, in which both pressures are raised. It has been recently pointed out that in all cases the blood pressure in the leg arteries, such as the femoral, is very much in excess of the brachial—a point which may be used in differential diagnosis, as it is not known to occur in other cardiac cases.

To the extra amount of blood which the left ventricle holds at the end of diastole is due (from increased stretching) the hypertrophy which follows aortic regurgitation. If the insufficiency is small, then perhaps the cavity is not dilated sufficiently to give any change in the bulk of the left ventricle; hence occasionally a slight amount of aortic regurgitation may be present without any obvious enlargement of the heart (Krehl). When slight regurgitation is present, even though hypertrophy is marked, compensation may be maintained for many years, as may be seen in aortic regurgitation from rheumatic endocarditis. In a pure valvular lesion, which can, however, seldom be supposed in rheumatic cases,[1] the limits of cardiac reserve power, as has been shown by Romberg and Hasenfeld,[2] are little if at all lowered.

Symptoms.—These are best considered under certain groups of cases:

1. **Latent.**—It is surprising how often in the routine examination one meets with aortic insufficiency that has never caused any symptoms. Even in quite young men with no history of rheumatic fever the condition may be detected accidentally, as in the examination for life insurance. Such patients may continue for years doing the ordinary work of life without the slightest inconvenience. A physician consulted me (W. O.) in whom the late Dr. Donaldson, of Baltimore, an expert auscultator, had recognized aortic insufficiency thirty-five years previously. After a very arduous life it had begun to trouble him, and he had slight attacks of angina pectoris.

2. **Acute Aortic Insufficiency.**—In rheumatic fever, in septic conditions, and following a trauma, acute insufficiency may arise. The general features of endocarditis are usually present, fever, sweats, etc. There may be nothing to attract attention to the heart itself. Palpitation or

[1] See Aschoff and Tawara, *Grundlagen der Herzschwache*, Jena, 1906.
[2] *Arch. f. Exp. Path.*, Leipsic, vol. xxxix, p. 333.

tumultuous action may be complained of, and occasional pain. As the condition grows worse there may be attacks of oppression of breathing, and even dyspnœa, but it is surprising, even in severe cases of ulcerative endocarditis, how slight may be the symptoms pointing to the heart. The physical signs are usually well marked—the rapid, forcible action, the throbbing vessels, and, under observation, the signs of insufficiency may increase. In some of the rheumatic cases it may be months before the compensation is established and before the patient is able to get up and move about comfortably and take exercise without shortness of breath. Even in cases that look the most hopeless, with extreme insufficiency and widespread tumultuous action of the heart, the severe features may gradually subside. One friend, of whose life, indeed, we despaired in 1884, in his second attack of rheumatic fever, survived and practised medicine for nearly twenty years. In other cases the acute insufficiency results from rapid destruction of the valve segments in a septic endocarditis, and the picture and course are those presented by this disease.

Some of the cases of the *syphilitic* aortic insufficiency come in this category. The patients are young men, and within a year or two of the primary infection, usually with the symptoms of angina pectoris, the aortic insufficiency develops in connection with a localized arteritis at the root of the aorta. The symptoms may disappear with antisyphilitic treatment, but the senior writer has not met with an instance in which the murmur of aortic insufficiency has been lost.

3. **Cases with Broken Compensation.**—For years before the breakdown occurs the patient may present a suspicious pallor of the face, the so-called aortic facies. Pronounced vertigo, or on exertion a ringing in the ears, may recur at intervals for months. Shortness of breath on exertion, attacks of nocturnal dyspnœa, uneasy fluttering sensation about the heart, or attacks of palpitation may initiate the breakdown. The pulse becomes somewhat rapid, is feebler, and sometimes irregular; the respirations increase; there are signs of congestion at the bases of the lungs, the liver may be enlarged, and the signs of venous stasis gradually develop; there may be slight œdema of the feet, but general anasarca is rare. The breakdown may be associated with attacks of cardiac pain, anginal in character. Some of the old hospital patients are admitted ten, fifteen, or even twenty times, always with the same symptoms, shortness of breath, cough, signs of engorgement at the bases of the lungs, albuminuria, and perhaps slight œdema of the feet. In some cases there is marked anemia. Dyspeptic symptoms are common, and the attack may begin with nausea and vomiting, which may remain troublesome features throughout. *Mental symptoms* are perhaps more commonly met with in aortic insufficiency than in any other form of heart disease. Delusions may occur even without any loss of compensation. More frequently with the breakdown, the patient begins to lose his mental control, and all sorts of delusions arise, particularly relating to time and place. In the endocarditic form, seen most frequently in young people and often in combination with a mitral lesion, the picture may be that of a slight gradual asystole with venous stasis and dropsy.

Fever, when present, usually indicates either a recurring endocarditis of the sclerotic valves or the presence of a complication.

Physical Signs.—Inspection.—Aortic insufficiency is the only valvular lesion which we can recognize at sight. There is no other condition with which so distinctive a type of throbbing of the arteries is associated. The beating of the carotids above the collar, the visible throbbing in the peripheral arteries, such as the radials and the temporals, and, on ophthalmoscopic examination, the retinal arteries. The peculiar jerk of the foot when the knee is crossed may suggest the diagnosis. Even the head may jerk with each systole. There are one or two conditions which simulate it, which will be referred to later.

Heart.—In children and in young persons the precordia may bulge. In the arteriosclerotic variety there is rarely any deformity of the chest. As the left ventricle reaches a very large size, the apex beat is dislocated downward and outward and is usually in the sixth interspace, sometimes in the seventh, and an inch or even two inches outside the nipple line. With full compensation it is regular, forcible, often punctuate, but when the dilatation is extreme and the muscle begins to fail, the impulse is diffuse, often wavy. Although the heart is so large, and, as seen by the fluoroscope, so low, it is very rare that pulsation occurs beneath the costal border in the nipple line. Localized pulsation may be present at the ensiform cartilage and there may be a diffuse impulse extending up the left of the sternum. In children the action of the heart may be very tumultuous. In ordinary cases no pulsation is visible at the base, but with extreme anemia or when the insufficiency has been rapidly produced, as in ulcerative endocarditis, there may be remarkable pulsations over the aorta and extending into the neck and along the course of the subclavian arteries. These are the cases in which, as Corrigan observed, the diagnosis of aneurism is usually made. And it is often difficult not to make such a diagnosis when one sees a definite impulse in the second or third right interspace, a violent throbbing in the supersternal notch, and the whole front of the chest shaken with each systole.

Arteries.—By inspection of the arteries alone the diagnosis may often be made. The subclavians and carotids throb violently, and there may be a visible pulsating tumor above the sternal notch. The brachials are visible, sinuous in their course, and with each systole they expand rapidly and as quickly collapse. Similar large pulsations may be seen in the radials and the temporals and even in some of the smaller vessels. In no other state do we see such widespread and peculiar throbbing in the peripheral arteries. Occasionally this diffuse vascular impulse is evident in the solid organs, as the liver and spleen, in which a pulsation may be felt, and the whole pharyngeal region may throb visibly and change in color with each systole. The beating in the retinal arteries may be forcible and even be distressing to the patient.

Capillaries.—The capillary pulse, first pointed out by Quincke, is seen in a great majority of cases. It may be looked for on the nails, or a line may be drawn on the skin, or it is well seen by the pressure on a bit of glass upon the lip. The finger nail is a very satisfactory locality

to see it, but it requires good eyes and always good light. Occasionally it is present in a very remarkable form. The palms of the hand blush with each systole and become pale in diastole. Held up against the light the change in color of the skin may be visible six or eight feet away. In some cases the length of the tongue when the mouth is open may be seen to increase at each systole.

Veins.—Pulsation in the cervical veins is common, but it may be difficult to distinguish from the communicated throbbing of the violently beating carotids. The superficial veins are often very full, and it is one of three or four conditions in which pulsation is common, particularly on the back of the hand and in the veins of the arm.

Palpation.—Depending upon the stage of the disease, the cardiac impulse is felt to be forcible, punctuate, heaving at the apex, or, when compensation fails, widespread, wavy, and diffuse. The whole front of the chest may be lifted during systole of the huge heart. The shock of the sounds at the apex is occasionally felt. A systolic thrill is rare at the apex. A thrill is sometimes present with the qualities of the mitral presystolic thrill, and it may even terminate abruptly in a first sound. In the endocarditic type of the disease, with the associated stenosis, a thrill is not uncommon at the base, more commonly systolic, but sometimes double. A very marked diastolic thrill may be caused by a calcified spur in the valve.

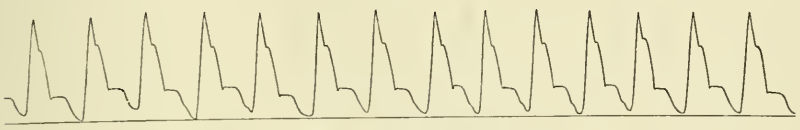
The arteries feel large and are very commonly sclerotic. From the character of the pulse alone the diagnosis may be often made. Even the handshake may suggest the lesion, or the characteristic quality may be perceived by touching the foot of a patient as he rests in bed. The pulse beat (pulsus celer) is sudden, forcible, and then drops immediately, resembling the beat of a water-hammer (water-hammer pulse). The abrupt shock-like sensation communicated to the finger is followed by a suden collapse—hence the name *collapsing pulse.* By elevating and grasping the arm about the middle, the palm of the hands toward the radial and ulnar arteries, the jerking quality is best perceived. It may be felt in the finger tips and even in the toes. The hand laid upon the dorsum of the foot may feel it with great distinctness. With anemia it becomes very marked. The pulse is regular, except during certain complications and toward the close when the heart muscle fails. The sphygmographic tracing is very characteristic—a straight and high line of ascension showing the abrupt and forcible distension of the artery, a rapid line of descent forming a very acute angle with the upstroke.

A thrill may sometimes be felt over the larger vessels. At the root of the neck the arteries may feel very voluminous, and even in diastole may be so distended, particularly in young persons, that the diagnosis of aneurism is made.

Auscultation.—A diastolic murmur is heard at the base of the heart, of maximum intensity over the sternum opposite the second or third interspace, sometimes at the left border of the sternum at the third or fourth costal cartilage. Authors differ very much in assigning the point of maximum intensity to this murmur. The French, particularly, place it at the right border of the sternum. The truth is it varies greatly in

different cases. In the endocarditic form and when stenosis is present the murmur may be most intense at what is known as the aortic cartilage. In the arteriosclerotic form, particularly when the murmur is soft, the maximum is more commonly at the left border of the sternum in the third or even the fourth interspace. The variation has been thought to depend upon the position of the insufficient segment. No murmur may be present to the right of the sternum in the situation at which one usually listens. The murmur may be so soft as to be readily overlooked, or it may only be rendered audible by exertion. A diastolic murmur

FIG. 12

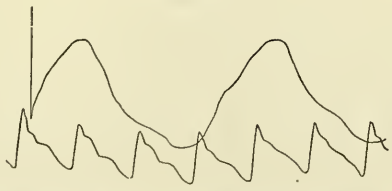


Aortic regurgitation. The pulse tracing shows a rapid rise and fall.

may disappear under observation, or it may change its character. In a few cases, though insufficiency is present, a diastolic murmur is not heard. In personal experience this has been very rare, but it may occur in the arteriosclerotic form. On several occasions the senior author heard a soft diastolic murmur, when postmortem, the valves by the water test appeared to be competent; but in these cases the segments were a little sclerotic, and there may have been dilatation of the aortic ring.

The *quality* of the diastolic murmur varies greatly in different cases. It may be a soft-drawn murmur, only just audible, or an intense blowing murmur, while in other cases it has a musical quality. In a majority

FIG. 13



Aortic regurgitation. The pulse tracing shows the effect of arteriosclerosis on the collapsing pulse, the fall being rendered much less sudden because of the increase in the peripheral pressure.

of the cases there is a double murmur; in the endocarditic form the systolic is usually rough and rasping in quality, in the arteriosclerotic it is soft. A systole bruit is not always present. The normal aortic second sound may be audible, but in a majority of cases it disappears altogether. The murmur is propagated down the sternum, and may even be intense at the ensiform cartilage. As a rule, it is not audible beyond the left parasternal line at the level of the fifth rib. In the common cases of the arteriosclerotic form it is not heard up the sternum or in the vessels of the neck. When there is dilatation of the aorta and

much roughening of the intima, the diastolic murmur may be well heard at the base of the sternum and in both carotids. So also the loud, rough, systolic murmur in connection with aortic stenosis may be transmitted upward. Change in posture does not, as a rule, make very great difference, except intensifying the murmur. Occasionally the alteration from recumbent to erect position may bring out a musical quality.

A systolic murmur of mitral insufficiency is present with the combined aortic and mitral lesions in the endocarditic group, particularly in children; in the arteriosclerotic group when the mitral segments are themselves curled and shortened, and with great dilatation of the ventricle when relative insufficiency of the valve occurs.

The Apex Diastolic Murmur (the Flint Murmur).—In a majority of cases of aortic insufficiency, as the stethoscope is passed along the fifth rib just beyond the parasternal line, a change is noticed in the character of the murmur during diastole. The soft blowing character is lost, and as the nipple line is approached a murmur is heard with a rumbling, purring quality, at once suggestive of the well-known one heard in mitral stenosis. Austin Flint, who first described this murmur, was astonished to find at the postmortem on two cases in which it was present that mitral stenosis did not exist. It has been studied with great care by numerous observers, and for many years at the Johns Hopkins Hospital our attention was specially directed to it, in connection with the very rich material at our disposal. The results have been published in a paper by Thayer.[1] The murmur is common, being heard in slight grades in a majority of cases. It is apical in situation, usually above and to the inner side of the maximum apex beat. It is often very localized. It may occur throughout the entire diastole or through the terminal portion, being purely presystolic, or in some instances it is distinctly mid-diastolic. The striking feature is its rumbling and vibratory quality, such as is so distinctive in the presystolic murmur of mitral stenosis. Sometimes there is a crescendo character, and it may terminate abruptly in a sharp snapping first sound. When to these features are added a thrill and a shock of the first sound felt on palpation, it is not surprising that the diagnosis of mitral stenosis is made. Time and again under these circumstances we have discussed the possibility of the existence of mitral stenosis, every cardiac physical sign of which was present. This difficulty is apt to occur in young persons with the endocarditic form, in whom the possibility is always present of the involvement of both orifices. In the arteriosclerotic form and in the subjects of syphilis the chances are always against mitral stenosis, even with a combination of physical signs which almost compels the diagnosis.

Auscultation of the Arteries.—Along the subclavians and carotids the diastolic murmur may sometimes be heard. Occasionally the double murmur is transmitted. As a rule, in the arteriosclerotic form the diastolic murmur is not heard above the level of the second costal cartilage, and is not transmitted into the arteries. The most characteristic phenomenon over the larger arteries, particularly the femoral, is the

[1] *Amer. Jour. Med. Sci.*, 1901, vol. cxxii, p. 538.

"pistol-shot" sound, a short, sharp systolic shock, and, as Traube pointed out, a second sound feebler than the first, coincident with the diastole of the artery. The latter is not always heard. With very slight compression of the artery, particularly at the femoral, a double murmur is heard—Duroziez's sign.

Diagnosis.—No heart affection is so easy to recognize, and there is not one less frequently overlooked. The diastolic murmur, and the visible collapsing pulse are pathognomonic. The mistake most likely to arise is the one mentioned by Corrigan in his original paper, namely, the diffuse throbbing of the aorta and the large vessels suggest aneurism. The diagnosis will be considered under that section. A diastolic murmur at the base is heard in several other conditions. Insufficiency of the pulmonary valves occurs in a few instances in connection with long-standing mitral disease. The conus arteriosus and the ring of the pulmonary artery are dilated, and there is relative insufficiency of the valve. The murmur is sometimes called after Graham Steell, who has called special attention to this lesion. It is more often diagnosed than existent. In several cases in which we thought it to be present in young persons the lesion proved to be aortic. The situation in the left intercostal space close to the sternum is of no moment whatever, as this is a common situation for the aortic diastolic murmur. The two important points really are the existence of old mitral disease and the absence of the characteristic vascular phenomena of aortic insufficiency. A diastolic murmur heard over the sternum may be of venous origin, and is met with particularly in Graves' disease. Cases have been described, too, in young persons in whom no definite cause could be assigned. Some of these cases may have been due to pressure of glands on the veins. Occasionally the *cardiopulmonary* murmurs are diastolic, and to this class in all probability belong the so-called transitory diastolic murmurs which are reported at intervals in the literature.

Rupture of the valve is indicated by a sudden onset after exertion, with pain, tumultuous action of the heart, and a loud, perhaps musical, diastolic bruit. The arteriosclerotic form is rare under thirty-five years of age. It is associated with signs of arterial disease, and the etiological factors are drink, hard work, and the stress and strain of life, or syphilis. Endocarditic cases occur in the young with a history of rheumatism or of some severe infection. More frequently than in any other form the orifice is narrowed, and there is a loud, rasping, systolic bruit. Relative insufficiency occurs in connection with dilatation of the aorta or with aneurism. The murmur is usually soft, and it may be heard high on the sternum, and with extreme atheroma a systolic murmur is usually present. In very old persons the insufficiency and stenosis are usually combined, and there is a rasping systolic murmur with a thrill.

Special Features and Accidents of the Disease.—Aortic insufficiency is a disease of accidents and surprises. Sudden manifestations may occur after a long period of latency. Among these the following are the most important: (1) The sclerotic aortic valves may be attacked by *endocarditis*, which may assume the ulcerative form. (2) In the sclerotic variety, in which the root of the arch and the coronary arteries are very

apt to be involved, *angina pectoris* is a common event, and death may occur in the first attack. In the syphilitic form, recurring attacks may precede the insufficiency, the process of which may be gradually traced. (3) *Sudden death* is more common in aortic insufficiency than in any other valvular disease. It may occur while the patient is at rest, even while asleep; more frequently it follows a sudden exertion or a violent emotion. While it may be due to acute dilatation, it is more probable that in a considerable proportion of the cases the coronary arteries are involved and there is a sudden interference with the circulation of blood in the heart muscle itself. (4) *Embolism* is not so common as in mitral disease. A vegetation growing on the sclerotic valves may be dislodged and plug a cerebral vessel, or a calcified fragment or an atheromatous flake may become detached and pass to the brain or to one of the peripheral arteries. In one instance the formation of a popliteal aneurism followed the dislocation of a fragment from the valve, which had been associated for years with a musical diastolic murmur. Following the accident the quality of the murmur changed entirely.

Prognosis.—Recovery is stated to occur, even by observers so careful as Potain, Leyden, and Gerhardt. Personally, the senior writer has never seen a case in which the diastolic murmur has disappeared, although in several syphilitic patients it has become very much less definite. It does not seem likely, as has been suggested, that when only one valve is affected the other two could enlarge and so compensate for the the defect. The prognosis varies with the different varieties. The endocarditic is the most hopeful, except in young children with a combined mitral lesion; but in young men compensation may be perfect, and for years there may be no symptoms. After an active life the patient may reach a good old age. Recurrent endocarditis, the chronic septic form or the rheumatic variety, may attack the valves, but such a patient may go through serious illness, even severe rheumatic infections, and recover with a useful heart. In the syphilitic form, the prognosis is bad, unless an early diagnosis is made and prompt treatment given. In the arteriosclerotic form, which comes on after the fortieth year, the prognosis is bad, as the root of the aorta and the orifices and the trunks of the coronary vessels are apt to be involved, so that the nutrition of the heart is soon interfered with. These are patients in whom sudden death is apt to occur.

Both in the young and in the aged, moderate stenosis lends a rather more favorable prognosis to the condition. Combined with mitral insufficiency, due to disease of the valve, the outlook is not so good. In adults, slight relative insufficiency of the mitral is a favorable feature.

STENOSIS OF THE AORTIC ORIFICE.

This is the rarest of all forms of valvular disease, and usually with it is associated some grade of insufficiency.

Incidence.—In the Edinburgh Infirmary Statistics, it occurred alone in 40 cases out of 1914, and in 152 cases with another lesion. Among

670 cases of valvular disease Romberg found only 28, among which there were only 17 without simultaneous disease of other valves.

Etiology and Morbid Anatomy.—As a rule, the process is chronic, but in a few cases one meets with an acute stenosis due to the growth of very luxuriant vegetations on the valves. There are two great types of the disease, the endocarditic and the arteriosclerotic.

Following *endocarditis* from any cause, but more particularly from rheumatic fever, the vegetations organize, the edges of the valve thicken, become adherent, sclerotic, and finally calcareous. The segments may be infiltrated with lime salts, and even the aortic ring itself, the whole forming a rigid, calcified mass perforated at one spot by a rounded, oval, or linear orifice. Very varying degrees of involvement of the segments are met with. As a rule, they are greatly deformed, but sometimes only the margins are diseased, and the narrowing results from the calcified nodular outgrowths. Indeed, Rendu, quoted by Barié, reports a case in which the narrowing was due to an enormous hypertrophy of the nodules of Arantius. The degree of stenosis is very variable, and may reach a remarkable grade, so that the orifice is not more than a few millimeters in diameter. Insufficiency is always present, the degree depending on the size of the orifice. Of course, when there is calcification and rigidity, there is no possibility of closure of the orifice during diastole. In this endocarditic form the aorta itself is not involved.

In the *arteriosclerotic* type the lesion of the valve is part of a widespread arterial degeneration. In men at the middle period of life the sclerosis is not often associated with stenosis. Occasionally there is a slight grade, but one may examine anatomically 25 or 30 cases of sclerosis of the aortic valves in succession without any narrowing of the orifice. In a few cases the edges of the valves coalesce and some narrowing results from atheromatous changes with calcification. The most characteristic form of arteriosclerotic stenosis is seen in elderly persons. It comes on insidiously, and may attain a very pronounced grade without causing any symptoms. In a special variety, described by Norman Chevers, the stenosis does not involve the ring, but the infundibulum or the part below it. Thus usually follows an extension of a chronic mitral fibrosis.

The heart is enlarged, sometimes very greatly, but rarely reaching the size of that of pure insufficiency. Early in the disease there may be pronounced hypertrophy without much dilatation, and clinically the enlargement may not be very great. Theoretically, with an obstruction at the aortic orifice, the ventricle is unable to expel the usual amount of blood into the aorta. The cavity at the beginning of diastole still contains blood, so that at the beginning of systole it is fuller than normal. This causes a greater stimulation of the muscle fibres of the walls, more pressure per unit area is exerted on the contained blood, and more is forced into the aorta through the obstruction. The stimulus of a resistance to contraction during its activity, *i. e.*, when the muscle is overloaded, causes systole to be prolonged from 7 to 30 per cent. of the normal. This differs from the conditions in aortic regurgitation, in which the systole is little if at all prolonged. In this, however, there is no extra resistance to contraction during the period of activity. If the

extra force expended by the ventricle is sufficient to discharge the normal amount of blood into the aorta, the cavity is not increased in size, and with the development of hypertrophy the circulation goes on as before. But if the stenosis is greater than can be overcome by the ventricle, or if the muscle of the ventricle is enfeebled, there is residual blood at the end of systole and the ventricular cavity is permanently enlarged. A third stage is that in which not only the ventricle but also the left auricle is overfilled at the beginning of systole. The auricle, by increasing the vigor of its contractions, may for a time be able to cope with it, but further failure may set in, leading to the same series of changes as occurs in mitral disease—congestion of the lungs, hypertrophy followed by failure of the right ventricle, venous engorgement, and œdema.

The estimation of the blood pressure in aortic stenosis shows that little if any difference exists from the normal. The number of recorded cases is, however, not great. We should expect to find that the maximum and minimum blood pressures estimated by reliable instruments were nearer one another than in a normal person.

Symptoms.—No heart lesion is more frequently latent. In the arteriosclerotic form, years may elapse before the patient experiences any discomfort. Indeed, it is one of the diseases, to use an expression of Oliver Wendell Holmes, that may promote longevity. It has helped many a man to become an octogenarian. In young persons, following endocarditis, symptoms on the part of the heart are more frequent—palpation, irregularity, distress on exertion, and the cardiac reserve is readily exhausted. It is not always easy to separate the effects of the aortic from the mitral disease, if present. In old persons, vertigo is a common symptom, and shortness of breath on exertion. An extraordinary degree of muscular vigor and good health may be maintained, but the capacity for exertion is greatly reduced, and breathlessness follows any extra effort. Attacks of angina occur in some cases, in one of which death may take place. Many patients have a sense of oppression and distress beneath the sternum on the slightest exertion or emotion. Cardiac failure may occur with venous stasis and all the signs of cardiac dropsy. Sudden death is not very uncommon. In others, intercurrent affections, such as cystitis and a consecutive nephritis, may cause death.

Physical Signs.—Inspection.—In young persons the precordia may bulge and signs of hypertrophy are present. In these cases the degree of enlargement of the heart depends much more upon involvement of the mitral and the amount of insufficiency of the aortic cusps. When these are present, there may be a great deal of dilatation and a very large heart. On the other hand, with pure stenosis there may be little or no hypertrophy, and the apex beat may be dislocated a little down and out, but the organ is not greatly enlarged. On palpation, the apex beat is easily felt in the fifth or sixth interspace, forcible and regular. Many years ago Traube pointed out that in a considerable number of cases the apex beat was absent.

Percussion.—Percussion shows slight increase of the cardiac dulness downward and to the left, varying with the degree of dilatation. On *palpation*, a systolic thrill is felt at the base, of maximum intensity in

the second right intercostal, propagated up the sternum and sometimes felt in the carotids and subclavians. On *auscultation*, a loud, rough systolic murmur is heard, of maximum intensity at the base. It is harsh, rough, rasping, usually protracted; in other instances high-pitched, whistling, and musical. It is propagated along the vessels of the neck and along the subclavians. It is sometimes heard with great intensity toward the apex of the heart, even when there is no mitral disease. The first sound is usually absent or very feeble. The second aortic sound is, as a rule, absent or replaced by a diastolic murmur, of varying intensity and quality. Sometimes the second sound is quite well heard, but it depends on the measure of retention of the elasticity of the aortic segments. It is not probable that with uniform calcification and rigidity, any sound could be produced. A peculiarity, more commonly met with in aortic stenosis than any other valvular lesion, is the murmur audible at a distance from the chest wall. This was noted by Stokes in the case of a politician in whom the murmur was so loud that it could be heard by his colleagues sitting about the table. Very many such cases are reported in the literature.[1] The pulse in aortic stenosis is slow, small, hard, and regular. The rate does not often fall below 60, and occasionally it is permanently at 40. In the senile cases, the Stokes-Adams syndrome may be present, and syncopal attacks or epileptiform seizures occur. The pulse is small, because the orifice permits of a comparatively small amount of blood, and the smallness of the beat may contrast in a striking manner with the force of the cardiac pulsation. Hardness is, as a rule, associated with the sclerosis of the vessel. Sphygmographic tracings are very characteristic, and show a small pulse wave, with a rounded or flattened summit, with a very oblique line of ascent, and almost without dicrotism.

Diagnosis.—The disease is frequently diagnosed when it does not exist. To inexperienced observers any loud murmur at the base suggests stenosis, whereas that lesion is the last to be considered. Slight roughening of the valves, roughening of the intima of the aorta, and hemic conditions are common causes of the systolic murmurs at the aortic area. With aneurism, too, a loud murmur is occasionally present. Stenosis of the pulmonary orifice has very much the same features on palpation and auscultation, but it occurs, as a rule, in young persons, the murmur is not propagated to any extent into the vessels of the neck, and is loudest to the left of the sternum.

Prognosis.—In young persons it is bad, particularly with associated mitral disease. Sometimes in the pure aortic stenosis following rheumatic fever the compensation may be maintained for many years, but, as a rule, the outlook it not so good as in the late sclerotic form of insufficiency. In any case, it is a lesion that takes many years for its formation, and many patients succumb to accidents, not to the disease itself. The most favorable cases are those in which, as a result of a slow, presenile sclerosis the orifice has been gradually narrowed. If the patient accepts the conditions, lives a peaceful, easy life, the heart lesion itself may promote longevity. For many years the senior writer followed with interest the

[1] See Ebstein, *Deutsch. Archiv f. klin. Med.*, Band xxxviii.

lives of two old men with typical features of aortic stenosis. One was an Anglo-Indian who lived to be over ninety years of age. He had a very large heart and a thrill at the base which could be felt through his overcoat and the murmur was audible some distance from the chest wall. The other died at the age of ninety-two years, of bladder complications. The patient was about sixty years of age when the aortic stenosis was diagnosed by Walshe.

Loss of compensation is usually the result of myocardial changes, and once gone is rarely restored.

INSUFFICIENCY OF THE MITRAL VALVES.

When from any cause the mitral segments do not close during systole of the ventricle a variable, amount of blood passes back into the left auricle through the insufficient valves. This is one of the most common of all cardiac lesions. In the Edinburgh figures, already quoted, among 1914 cases there were 585 with mitral insufficiency alone, and 463 in which it was combined with another lesion, in 231 of these this being mitral stenosis.

Forms.—There are three great groups of cases, the *endocarditic*, the chronic *sclerotic*, and the *relative* or muscular. In a few cases the insufficiency may follow rupture of one of the segments.

Endocarditic Form.—This, the most common, is met with in young persons as a complication of the acute infections, more particularly of rheumatic fever. The general effect of endocarditis upon the valves has already been described. The special danger of the rheumatic form is owing to the fact that the segments are the seat of a productive valvulitis. In certain cases, insufficiency is rapidly produced by destructive lesions which erode the chordæ tendineæ and destroy the segments, so that within a week or ten days a high grade of insufficiency is produced. In a large proportion of all cases there is no actual erosion of the valve itself, but the insufficiency is caused by a gradual shrinkage of the newly formed connective tissue in the substance of the valve. When this goes on very rapidly, as is sometimes the case, both curtains are rolled up as it were, leaving a widely open orifice. This is not nearly so common as the slower process in which the constricting cicatrization draws together the margins of the valves, so that with the insufficiency there is some grade of narrowing. The orifice may admit the thumb, or not more than the tip of the little finger. The edges are smooth, greatly thickened, often of a cartilaginous hardness, and the chordæ tendineæ are greatly thickened, shortened, and often fused together. It is quite frequent to have beads of fresh endocarditis on the margins of the thickened valves. Lime salts may be deposited, and the valves and ring together form a solid calcified mass.

Arteriosclerotic Form.—In the arteriosclerotic form, without any preliminary acute endocarditis, the valves gradually thicken, the edges become curled, slightly shortened, the chordæ tendineæ become thickened, the orifice is slightly narrowed, lime salts are deposited in the valves, and, as age advances, the whole valve and ring become a rigid

and calcified membrane. In a slight degree, sclerosis of the mitral valve is met with in all persons over sixty years of age, and is an expression of the wear and tear of work.

Relative Insufficiency.—Relative insufficiency, by far the most common form, occurs whenever dilatation of the mitral ring reaches such a grade that the normal valve segments are no longer able to close it. Known by the names of functional, muscular, or, more commonly, relative insufficiency, the most common cause is loss of tone of the muscle which surrounds the mitral ring. This occurs in many blood conditions, such as chlorosis and pernicious anemia, in fevers, in many neurotic states, as neurasthenia, in Graves' disease, and in all cases when the dilatation of the ventricle from any cause reaches a certain grade.

Insufficiency due to rupture of the chordæ tendineæ, or of one segment, is very rare in the healthy valve, but a number of cases have been described; most frequently the chordæ tendineæ of the anterior segment are ruptured.

Symptoms and Physical Signs.—Many patients with mitral insufficiency never present any symptoms. In a still larger proportion symptoms are only present at the terminal stage of a long and silent history. The cases which give rise to symptoms earliest are those of insufficiency following the endocarditis in children, particularly in the tragic group which makes rheumatic fever so malignant an infection. Relative insufficiency in the fevers, in chlorosis, in anemia, may never give rise to symptoms. No valvular lesion presents such diversity of features in regard to the duration and severity. There are cases in children in which the valve segments are rapidly curled and rendered so insufficient that the limits of compensation are quickly reached. On the other hand, there is no valve lesion in which we see more perfect and more enduring compensation. The marvellous manner in which the heart is able to carry on the work illustrates the remarkable response of muscle to calls made upon it very gradually. It reminds one of Montaigne's illustration of the force of custom: "He seems to me to have had a right and true apprehension of the power of custom, who first invented the story of a country woman who, having accustomed herself to play with and carry from the hour of its birth, a calf in her arms, and daily continuing to do so as it grew up, obtained by this custom that when grown to be a great ox she was still able to bear it."

Pathological Physiology.—Depending upon the degree of insufficiency of the valve, a variable amount of blood is forced back into the left auricle, during its diastole, and while it is filling from the pulmonary veins. With this extra amount of regurgitated blood the auricle reaches its normal distension sooner than previously. The pressure at the end of diastole is greater than at this period were there no valvular deficiency, the muscular fibres of the auricle are more stretched than normally, and, as we know from v. Frey's[1] experiments, the muscle is stimulated to a greater contraction. If the more powerful contractions, either immediately succeeding the lesion of the valves or ultimately by reason of

[1] *Deutsch. Arch. f. klin. Med.*, 1889, p. 358.

hypertrophy, can force into the ventricle the normal amount plus the extra blood which was regurgitated, the circulation becomes compensated and the effects of the insufficiency do not extend farther than the left auricle. Over and above the evidence of regurgitation by auscultation, very careful percussion may give a higher pitched note at the apex of the left lung in front, and with the *x*-rays a marked increase in the amplitude of pulsation in the position of the left auricle may be seen.[1] A method has recently been devised by Minkowski[2] for obtaining a graphic record of the pulsation of the left auricle, and this might be of use in determining the presence of increased activity of this chamber. The left ventricle must accommodate the additional blood from the auricle, and in consequence its cavity becomes larger, its pulsations (owing to the slight stretching) more forcible, and hypertrophy of the muscular walls follows.

In the condition just described it has been assumed that the normal closure of the pulmonary veins took place during the systole of the auricle. We do not know at present how this is accomplished, but from the analogy of the right auricle, in which muscular bands are disposed to that end, we may conclude that it is effected by the same process.[3] With further dilatation of the cavity, the orifices will remain open during the systole and the heightened pressure will be communicated to the blood in the pulmonary vessels. The dilatation of the auricle does not go beyond a certain point, partly because of the opening of the orifices of the pulmonary veins and partly from an increase in the connective tissue, which has been shown to accompany compensatory hypertrophy.

MacCallum and McClure,[4] in studying the effects of artificial lesions of the mitral valve in animals, have found that the pressure in the systemic arteries falls markedly, that in the left auricle rises, and that in the pulmonary artery may rise or fall; a high degree of insufficiency produces a fall of pressure in both the systemic and pulmonary systems; in slight insufficiency it usually rises. Whatever the pressure, the lungs invariably contain a larger amount of blood, for it has been shown that the venous pressure falls with a fall in the arterial pressure. The depletion of the systemic arteries is made up either by a constriction of the peripheral vessels, or by an increase in the volume of the blood. In the case of a small deficiency of the mitral valve the ventricle enlarges to receive the normal amount of blood from the auricle plus a portion of that regurgitated, and rejects into the aorta something less than the normal amount.

In what way the hypertrophy of the right ventricle helps is an open question. MacCallum and McClure have shown that, so far as the pressure is concerned, the lung capillaries may be looked upon almost as a rigid tube, for the pulsations of the left ventricle are transmitted directly to the pulmonary artery, and with such little loss of time that

[1] Abstract in *München. med. Woch.*, 1907, p. 849. See also Bonniger, *Deutsch. med. Woch.*, 1907, p. 333.

[2] *Deutsch. med. Woch.*, 1906, vol. xxii, p. 1248.

[3] Keith describes a very probable method of closure of the orifices of the great veins into the right auricle, *Lancet*, 1904, vol. i, p. 555.

[4] *Johns Hopkins Hospital Bulletin*, 1906, vol. xvii, p. 260.

the pressure wave of the left ventricle is opposed to the action of the right ventricle during the systole.

A mitral insufficiency compensated for ordinary conditions by the right ventricle may continue for a long period of years. If this chamber fails either from increasing deficiency of the mitral valve or from changes in its muscle, the tricuspid valve becomes incompetent. The right auricle becomes dilated and hypertrophied. The orifices of the veins are no longer closed during systole, and finally the pressure from the right ventricle is communicated to the venous system which becomes engorged. With great insufficiency of the mitral valve considerable pressure is communicated during systole to the auricle, whose walls probably become so stretched that the muscular fibres are injured and the contractions become very feeble. The increased pressure in the auricle and pulmonary bloodvessels gives rise to the thickened endocardium, so frequently seen in the former, and atheroma in the latter. In the first stage the left ventricle hypertrophies as a result of the increased pressure and compensatory dilatation at the end of diastole, caused by a more vigorous left auricle. Even with failure of the left auricle the pressure in it communicated from the right ventricle is sufficient to maintain the filling of the left ventricle, the hypertrophy of which may keep pace with the further dilatation, and it may become very large and thick. Under these conditions the normal filling of the arteries would be maintained, but with failure of the hypertrophy and loss of the contractile power of the muscle, the arteries become properly filled and the blood pressure tends to fall. With the lessened blood pressure comes an increase in the rate of the pulse. The cause of the irregularity of the pulse in mitral disease is unknown; possibly it is due to the same condition as that suggested by Mackenzie in mitral stenosis.

Little that is definite can be said of the blood pressure in mitral regurgitation. The condition of the pulse is no evidence of the height of the pressure estimated by clinical instruments, for cases are recorded with a blood pressure of 140 mm. Hg., in which the pulse was scarcely to be felt. Hensen[1] does not agree with v. Basch, who says that the blood pressure in mitral disease is low, for oftentimes, according to his observations, it is distinctly above the average. With any irregularity of the pulse the maximum blood pressure varies much, sometimes being only a little over 100 mm., at other times reaching 140 mm. or more. The feebleness of the pulse in mitral disease, when the pressure is high, may be due to peripheral constriction of small arteries to compensate for the underfilling of the arterial system, but of these peripheral mechanisms we have little knowledge.

Symptoms.—The symptoms may be divided into two groups. While compensation is still good, there are many minor manifestations, as the pain and breathlessness on exertion. When the insufficiency is extreme, the patients have a bluish tint of the cheeks and ears, giving the very suggestive appearance, the "mitral facies." The hands and feet may be blue, and in very long-standing cases the fingers may be clubbed.

[1] *Deutsch. Arch. f. klin. Med.*, 1900, vol. lxvii, p. 512.

Occasionally in children the degree of cyanosis reaches that met with in congenital heart disease, but it is never so extreme as in the cases of adhesive pericarditis with great hypertrophy of the heart and proliferative perihepatitis and peritonitis. Breathlessness on extra exertion may persist for years. These patients are especially liable to bronchitis in the winter. One of the most remarkable features is the recurrence, over long periods of years, of hemoptysis. In Philadelphia, the senior writer saw frequently a physician who had had his first attack of hemoptysis during the Civil War. Tuberculosis was then suspected, but a mitral lesion was discovered. On and off during twenty-five years he had had attacks of quite sharp hemoptysis, sometimes with great relief.

Broken compensation or decompensation may set in abruptly, following any extra exertion, a severe mental shock or a protracted illness. Palpitation, which objectively may have existed for years, becomes evident and distressing to the patient. The shortness of breath increases. The patient wakens at night, perhaps abruptly in a paroxysm of shortness of breath, or there may be distressing "sleep starts," in which, just as he is dropping asleep, he wakens gasping as though his heart had stopped. The most distressing single feature is the oppression in the chest associated with the breathing. The slightest exertion brings it on, and the patient may at last be unable to move from his bed, or the dyspnœa may continue even when he is at rest. Very soon the signs of venous stasis are present. There is œdema of the feet, which gradually extends upward; the abdomen begins to swell, the liver is enlarged, and there is a slight jaundiced tint to the skin. The anasarca becomes extreme and the serous sacs may become dropsical. The urine is scanty and albuminous, and contains tube casts and sometimes blood corpuscles. The patient is restless, often sleepless at night, and there is anorexia and sometimes vomiting. With judicious treatment, even with rest alone, the attack may pass off, and months, or even years, may elapse before a breakdown occurs. Only too frequently it happens that once compensation has been broken, the patient is very liable to subsequent attacks.

Among special features which may be mentioned are embolism, either from a clot in the left auricle or from a vegetation on the edge of the thickened valves. A remarkable thrombosis may occur in the distended veins, particularly in the jugular or in the brachials. There was an extraordinary case at the Johns Hopkins Hospital—a woman who was under our care for many years. She had half a dozen attacks of thrombosis in different parts of the body.

A remarkable feature of these very chronic cases of mitral insufficiency is the recurrent *hydrothorax*, most common on the right side, which may be the only feature, and there are instances in which the patient has been up and about, and able to attend to his work, but has had to be tapped every week or even at shorter intervals. Perhaps the most extraordinary case on record of this kind is reported by W. T. Gibb, of New York; a physician with combined aortic and mitral disease was tapped 311 times in 580 days, but was able to be up and about and do almost anything, until two days before his death.

The *hepatic* symptoms of heart disease are met with in the most typical forms in mitral insufficiency. With the establishment of tricuspid insufficiency there is a swelling of the organ, the edge of which may be felt a hand's breath or more below the costal border. On careful inspection, diffuse pulsation may be seen, and the organ may be felt to swell with each systolic impulse. A slight tinge of jaundice is common. In the long-standing cases, the liver becomes greatly enlarged, the connective tissue increases and the state of cardiac cirrhosis is gradually produced. The organ is large, smooth, and hard, with rounded edges. In very protracted cases shrinkage may occur. In an interesting group of cases for a year or more toward the close, the features are entirely hepatic and the patients come under observation with recurring ascites, which may require tapping every few weeks. This accumulation of fluid in the peritoneum may be the only form of dropsy present. While it is not always possible to exclude the influence of alcohol, yet there are cases in which the cirrhosis seems to be altogether a late effect of the stasis.

Physical Signs.—Inspection.—In children the precordia may bulge and there is usually a very large area of visible pulsation, undulatory along the left sternal border with a more definite apex beat in the fifth or sixth, sometimes the seventh, interspace. There may be visible pulsation to the right of the sternum and a marked impulse in the second and third left interspace. Frequently the whole front of the chest throbs visibly, and in mitral insufficiency we see more widespread impulse than in any other cardiac condition. The visible heart beat may extend from one anterior axillary line to the other. The impulse is usually very strong at the ensiform cartilage, and the heart may be so depressed and enlarged that there is a forcible, punctuate impulse of the right ventricle below the left costal border in the parasternal or even the nipple line. In the arteriosclerotic type, in elderly persons, with very slight hypertrophy of the left ventricle, the impulse may be scarcely visible. In very long-standing cases, the apex beat may be far out, even in the midaxillary line. In relative insufficiency, the impulse may be scarcely visible, and may be only a little, if at all, to the left of the nipple line.

The veins at the root of the neck are usually full, and there are the pulsations, which will be more fully described in connection with tricuspid insufficiency. In the stage of decompensation, at the jugular bulb, just above the right sternoclavicular joint, there may be a large ovoid tumor as big as an egg.

Palpation.—The degree of shock will depend upon the extent and force of the cardiac impulse which may be very strong and heaving. A systolic thrill at the apex region and transmitted into the axilla, is not so common as the presystolic in mitral stenosis, but in the long-standing cases in adults it may be very rough and rasping. The shock of a first sound is rarely to be felt, but the shock of the second may be widely diffused.

Inspection and palpation are the only safe guides in estimating the organic character of mitral insufficiency; if the apex beat is dislocated outward and very forcible, we may be certain that there is an actual lesion present.

Percussion.—The cardiac dulness is increased, particularly in a lateral direction, and may extend far to the right, reaching even to beyond the parasternal or nipple lines. The upper limit may be at the second rib, and in extreme cases far to the left, even to the midaxillary line. Not even in the cor bovinum of aortic insufficiency do we find, particularly in children, such an extended area of cardiac flatness.

Auscultation.—A murmur accompanying or obliterating the first sound, of maximum intensity at the apex, and transmitted toward the axilla is the most distinctive single physical sign of insufficiency of the mitral segments. Its quality may vary from a soft blowing to a loud, harsh, rasping murmur; or it may have a distinctly musical quality, which is perhaps more frequently heard with mitral insufficiency than in any other lesions. The point of maximum intensity is, as a rule, at the apex or a little inside it. At times it is heard loudly along the right margin of the sternum and, as Naunyn pointed out, it may be even of maximum intensity at the second or third left interspace. The special direction of propagation is along the left pectoral fold into the axilla, and the murmur is often loud and distinct at the angle of the scapula. In long-standing cases with great hypertrophy the murmur may be heard all over the chest and even to the top of the head. With a murmur of any intensity the first sound is usually absent, but it is very variable and in many instances of relative insufficiency the first sound is well heard. The second sound at the base is greatly accentuated, particularly to the left of the sternum, over the region of the pulmonary artery. With failing compensation there may be a disappearance of the heart murmur and the condition of delirium cordis with a confusion of sounds.

The *pulse* in mitral insufficiency in the stage of compensation may be quite regular, but in the endocarditic group in children and in adults irregularity is almost always the rule. For years it may persist without any sign of cardiac weakness and with a normal blood pressure, and even when the pulse is very small and extremely irregular the patient may feel no inconvenience.

Diagnosis.—The recognition of mitral insufficiency is, as a rule, very easy, but it is not always so easy to determine the type of the disease. The endocarditic form in children, accompanied with great dilatation and hypertrophy, and often with other valvular lesions, presents no difficulty. Nor in adults, with the triple manifestations of a dislocated apex beat, a loud, rough, systolic murmur, and a greatly accentuated, pulmonic sound, is there any real difficulty. In the hypertrophied heart of chronic Bright's disease, in myocarditis from whatever cause, and in the relative insufficiency of anemias and toxemias, it may be very difficult to determine whether there is an actual lesion of the valve, or not. Usually the murmur in these cases is less intense, and shows marked changes in varying the posture of the patient. It may be present in the recumbent, absent in the erect position, and it may disappear entirely as the general condition improves, or as the dilatation of the heart subsides.

Prognosis.—Among valvular lesions it is at once the worst and the best. With the endocarditis of children, insufficiency may quickly reach a grade beyond the powers of compensation. On the other hand, a

slowly induced insufficiency, combined with a moderate degree of narrowing may become stationary, the edges of the valves calcify, the heart hypertrophy is well maintained, and the patient may live a long and useful life without any serious discomforts. It may be said that, as a rule, in children under ten the prognosis is bad, more particularly as they are apt to have recurring attacks of rheumatic fever, and the condition is not so much a valvular lesion as a general carditis. The older the individual at the time of the onset of the endocarditis, the better is the prospect. The arteriosclerotic variety may not diminish the expectation of life. Indeed it often happens that the discovery of a mitral bruit, at examination for life insurance, promotes longevity. Warned to be cautious, the patient takes better care of himself and avoids, so far as possible, stress and strain. In the cases of relative insufficiency the prognosis depends much more on the condition with which it is associated than on the valvular leak.

STENOSIS OF THE MITRAL ORIFICE.

Etiology and Pathological Anatomy.—The disease is most frequent in females. In 80 cases noted by Dickworth, 63 were in women. Of 196 cases at Guy's Hospital collected by Samways, 107 were females. In the Edinburgh Hospital statistics of 1914 cases of valvular disease, 304 were mitral stenosis alone, 231 were mitral stenosis and insufficiency, and 26 were mitral stenosis with an aortic lesion. The stenosis is frequently not present alone, and insufficiency in some grade is a very common accompaniment. In fact, it may be said that the classical malady described as mitral insufficiency is almost always associated with some degree of stenosis; while mitral stenosis, except in a few rare instances, always permits of regurgitation. Etiologically, there are three groups of cases: (1) Those which follow an acute *endocarditis*. This is the most common form, and it occurs in the young and particularly in young girls. Rheumatic fever is the dominant factor, and next to it chorea. Of 140 cases of chorea, examined at a period of more than two years subsequent to the attack, 72 had signs of organic disease of the heart, and 24 of these presented the physical signs of mitral stenosis. Scarlet fever, measles, and whooping-cough may be responsible for a few cases. It has been claimed that tuberculosis plays a certain rôle, but for this there is not much evidence. As to the influence of mitral stenosis on pulmonary tuberculosis there is much difference of opinion. The studies of Tileston[1] suggest that patients with mitral disease have a relative immunity to tuberculosis, and if it be present, the pulmonary disease is mild with a strong tendency to cure. In a second small group of cases the stenosis is the result of a *primary sclerosis* of the valve with thickening and adhesion of the edges, shrinking of the chordæ tendineæ, with widespread atheromatous changes in the substance of the valve and in the mitral ring itself. It is not always easy to determine whether or not these changes have been initiated by an endocarditis, but this group

[1] *Jour. Amer. Med. Assoc.*, 1908, vol. l, p. 1179.

occurs at the older period of life, and in men as well as in women. Newton Pitt has pointed out the frequency of association with chronic interstitial nephritis, 33 cases in 542 autopsies. Lastly, there is an important group of cases met with almost exclusively in women, in which *no positive factor* can be determined. The cases are usually latent, found accidentally, and the condition may persist for many years without causing any symptoms. In adult women, in whom this form is most common, one is almost always safe in putting the interrogative negatively—you have not had rheumatism. Some have thought that this form may be congenital, but this is unlikely, as it is rare to meet with lesions of the mitral valve during fetal life or immediately after birth.

A functional or spasmodic stenosis of the mitral is spoken of, due either to spasm of the sphincter muscle or of the papillary muscles. The cases have been described in hysterical patients, and in anemic and chlorotic subjects.

Anatomically, there are two forms, the pure or membranous, in which the left auriculoventricular ring is surrounded by a thin membrane representing the fused valve segments, perforated by a narrowed orifice which admits the tip of the little finger. The membrane is a little thickened, but it is pliable, the edges are smooth and may be readily placed in apposition, so that it is possible, during life, that the valve has been competent. These are the cases of what the French call *pure* mitral stenosis, and it is this form more particularly that is met with in women, in whom no history of rheumatism or other etiological factors can be found. From the auricle, this form presents a remarkable funnel shape. In the other variety, the valve segments are greatly deformed, the chordæ tendineæ thicken, and with the irregular calcified excrescences with atheromatous plates, the whole valve and ring are converted into a rigid mass, in the middle of which there is a linear slit or a rigid orifice that admits the tip of the thumb or index finger. The heart itself is not greatly enlarged, and may not weigh more than fourteen or fifteen ounces. In elderly persons the organ may, indeed, look small. The left auricle, as a rule, is greatly enlarged, and may hold several hundred cubic centimeters of fluid. Normally, the capacity in under 50 cc. Cases have been reported in which it has held 500 or even 650 cc. The appendix is usually greatly enlarged. The endocardium is very opaque, and when the dilatation is extreme, the walls are very thin and fibrous. In the early stages, as Samways pointed out, the hypertrophy of the auricular walls is very marked.

The chambers on the right side are much enlarged, the ventricle contrasting in a remarkable way with its fellow; indeed, the apex of the heart may be made up entirely of the right ventricle. While this may be said to be the rule in mitral stenosis, there are some instances in which this contrast is not so striking, and the left ventricle may also be hypertrophied. The right auricle is greatly enlarged and the tricuspid orifice is much dilated.

Pathological Physiology.—Much of what has already been said of mitral regurgitation is true also of mitral stenosis. An increase of auricular pressure occurs at the end of diastole leading to stimulation

and later to hypertrophy of the auricular muscles. Increase in auricular pressure, from further obstruction of the valves, causes such stretching of the muscle that increased action assisted by hypertrophy is not able to overcome the additional pressure. The orifices of the pulmonary veins now remain open during auricular systole, the pressure gradient in the pulmonary vessels becomes less steep and hypertrophy and increased action of the right ventricle follow as the result of the increased power required to empty the right ventricle. Mackenzie's view of the cause of the irregular pulse of mitral stenosis is now generally accepted. He has noticed that when the crescendo murmur of mitral stenosis fails, or is replaced by a low-pitched murmur, the irregular pulse appears; moreover, at the same time, the evidence of the contraction of the left auricle fails. In several cases that he has observed, over many years, the evidence of normal regular contraction of the auricle—a wave in the jugular pulse, a wave in the cardiograph, and a presystolic crescendo murmur—has not been present with an irregular pulse, or, as Mackenzie calls this particular form of irregularity, the *disorderly* pulse, from the absence of any rhythm in its irregularity. The condition is now known to be almost the invariable accompaniment of auricular fibrillation. In one case drawings of the heart compared with the normal, show enormous dilatation of both auricles. The explanation given, is that the auricular muscle has become so stretched that the normal impulse stimulating the ventricle to contraction, which comes from the entry of the great veins into the right auricle, is unable to reach the ventricle owing to the condition of the muscular fibres, and that the rhythm of the heart is now governed by the part of the conducting system of fibres (Tawara's Knoten) which lies nearer the ventricle and is not under such unfavorable conditions. In mitral stenosis the left auriculoventricular orifice is narrowed, hence, unless the auricular muscle is particularly strong, the ventricle does not receive as much blood as it should normally. This is especially so in the severer forms of stenosis. There is, therefore, no tendency to a dilatation or hypertrophy of the walls; in fact, with less inflow into the ventricle, the cavity tends to become smaller and the bulk of the muscles less. In experimental stenosis, produced either by constriction of the auriculoventricular groove by a ligature, or by introducing into the auricle a distensible balloon, the pressure in the systemic arteries falls; that in the left auricles and pulmonary artery rises. The blood pressure in man is not abnormally low; in fact, the same feature as has been noticed in mitral regurgitation may be present —namely, a very small pulse with a blood pressure slightly above normal. With good compensation there is but little departure from the normal, and when irregularity sets in, the maximum pressure varies considerably —in one of Hensen's cases from 105 mm. to 140 mm. Hg.

Symptoms.—*Latency* may be said to be the special feature of the disease. At a busy clinic, not a month may pass without meeting the most typical physical, signs in a person who has had no symptoms whatever. Even narrowing, of a shirt-buttonhole, size may be present, with nothing more than slight shortness of breath on exertion. In other instances, the patient for years has irregularity of the pulse and is short

of breath on exertion. We must recognize a large group of cases in adults, in whom the lesion is well borne for an indefinite number of years. In children it is different, particularly in the cases that follow rheumatic fever. There is very often failure of development. They remain feeble, the breath is short, they are anemic, and there is a liability to fresh attacks of endocarditis. Many patients present for years a slight cyanosis, more particularly of the cheeks and of the ears, and are liable to have recurring attacks of bronchitis.

The symptoms of cardiac breakdown are very much the same as in other forms of valvular disease. The irregularity becomes more marked, œdema of the feet and ankles occurs, the breath is short and the signs of stasis are present in the viscera. Brisk hemoptysis may occur, sometimes with relief. Among unusual symptoms is paralysis of the left recurrent laryngeal nerve by pressure of the enlarged left auricle. This, in connection with a wide area of impulse in the second, third, and fourth left interspaces, may lead to the diagnosis of aneurism. The senior writer has seen two cases of this kind, and others are reported in the literature.

Accidents in the disease are common, such as sudden attacks of congestion of the lungs and acute infarcts with hemoptysis. Sudden death in an acute cardiac failure may occur. Embolism is very common, the embolus being either a fragment of a clot from the dilated left auricle, or more frequently a fresh vegetation is whipped off from the orifice of the valve and plugs the left Sylvian artery, causing right hemiplegia and aphasia. In other instances there is embolism of the peripheral arteries. In rare cases, widespread thrombosis may occur.

Physical Signs.—Inspection.—Nothing may be noticed. The apex beat may be in the normal situation and the precordia does not suggest a valve lesion. The heart, indeed, may appear to be smaller than normal. In other cases, the apex beat is moved an inch or two to the left, the impulse is more forcible and there is marked pulsation in the parasternal line and in the lower sternum. In children, the precordia usually bulges, and there is marked pulsation in the interspaces along the left margin of the sternum, from the second to the fifth or sixth. In advanced cases, the pulsation of the enormously enlarged heart may be seen to the right of the sternum, but in pure mitral stenosis the hypertrophy of the heart rarely reaches the degree seen in insufficiency.

Palpation.—In a considerable proportion of all cases, when the lesion is well compensated, the diagnosis may be made by palpation alone. At the apex is felt a purring thrill—the *frémissement cataire.* It is limited in area, rarely felt above the fourth rib, most marked during expiration; occasionally only brought out after exertion. Coinciding with the diastole of the ventricle, it may be felt to extend throughout the whole period, or it is only in the latter part, rising crescendo-like toward the end and terminating in the sudden, sharp shock of the first sound. The localization, the occurrence in diastole, the purring, vibratory quality, and the abrupt termination in the first sound, form a quartet of signs that rarely lead us astray. As the disease advances and a stage of decompensation is reached, the thrill may disappear.

Percussion.—In the early stages there may be no increase in the area of cardiac dulness. With the increase of the left auricle, the flatness to the left may be increased, but the great enlargement is in the right ventricle, with extension of the dulness to the right of the sternum. The absolute cardiac flatness reaches high on account of the enlargement of the conus arteriosus. The great dilatation of the left auricle may compress the upper lobe of the lung, and the area of deep dulness may be much increased upward in the third and fourth interspaces. But the auricle itself rarely comes in contact with the chest wall. This enlargement of the auricle is well seen with the fluoroscope.

Auscultation.—In compensated cases, there is heard in diastole a rumbling, vibratory, or purring murmur, usually increasing in intensity and terminating abruptly in a loud, snapping, first sound. The special features of the murmur of mitral stenosis are: (1) Its *limitation:* the bell of the stethoscope may cover the region in which it is heard. (2) The *quality:* vibratory, grating, or a low, echoing rumble; with the exception of the rare instances of tricuspid stenosis, this quality of murmur is heard only at the mitral orifice. (3) The *sharp, valvular, first sound:* There are many modifications and changes. In the early stages of the disease there may be nothing more than a slight echoing rumble, and it is only on exertion that the characteristic murmur is brought out. Its position in diastole is variable. It may occupy the entire period, rising crescendo-like toward the close. It may be purely presystolic, occupying only the terminal portion and running directly up to the sharp valvular first sound. In other cases it is mid-diastolic, and the perceptible short interval separates it from the first sound. In this case it has to be carefully distinguished from the third sound of the heart which is frequently heard in normal persons, and especially under conditions of slight excitement. No other murmur may be present. A very soft systolic may be heard in some cases, with very slight extent of propagation. When decompensation is present, the typical presystolic murmur may disappear and a loud systolic is heard.

The state of the sounds of the heart in mitral stenosis is of exceptional interest. As already mentioned, the shock of the first sound is extraordinarily forcible. Except in certain neurotic states, no such snapping sound is felt at the apex. On auscultation, too, it is remarkably intense, and instead of a dull, thudding sound, it is of a flapping, valvular, even of an amphoric, ringing quality. So intense may it be that we meet here one of the few conditions in which the heart sounds are audible at a distance from the chest wall. It is common enough to hear the first sound a few inches away, but twice it has happened in my experience to hear a clear, bell-like first sound as I sat at the bedside of the patient. In one case Dr. Blake, of Baltimore, measured the distance, and found it a little over six feet. Naturally, this loud, ringing sound is propagated to the back. The second sound may be well heard at the apex, sharp and accentuated, increasing greatly in intensity as the stethoscope is passed toward the second left interspace. Here it is often reduplicated. In later stages the second sound may disappear at the apex, while it is loudly audible at the base. In the stage of decompensation, with great

irregularity and dilatation of the heart, the characteristic physical signs may disappear. Time and again the diagnosis of mitral stenosis is made for the clinician by the pathologist. A week's rest in bed with the use of digitalis may serve to bring back a presystolic murmur. In other instances a murmur of typical quality and a first sound of amphoric timbre may disappear and be replaced by a loud mitral systolic. An acute illness, a period of debility from any cause, may cause the murmur to become very feeble or even to disappear. In such instances there may be nothing but a faint diastolic rumble, which is changed into a more definite murmur on exertion.

In uncomplicated cases, no murmurs are heard at the aortic area. The first sound is usually very feeble in comparison with the second.

Diagnosis.—No valve lesion is more readily recognized than mitral stenosis. One has always to bear in mind that when the terminal stage is reached, and the patients are admitted with delirium cordis, the murmur is no longer present, and the diagnosis may be perhaps only suggested by the sex of the patient and by the fact that there is a somewhat snapping first sound. A murmur with the same quality during diastole at the apex, is heard in aortic insufficiency, known as the Flint murmur, and has already been discussed. In tricuspid stenosis a rumbling presystolic murmur is heard, of maximum intensity over the body of the heart. In the conditions in which the senior writer has heard it, mitral stenosis has always been present as well. And lastly, in a considerable number of cases of pericardial adhesion, a rumbling apical murmur is heard in diastole. It rarely has the peculiar limited localization, nor does it end in a snapping first sound.

TRICUSPID INSUFFICIENCY.

Etiology.—There are two groups of cases, one the result of organic disease of the valve cusps, the other relative or functional incompetence from dilatation of the tricuspid ring due to lack of tone (muscular insufficiency) in the right ventricle.

1. Organic disease follows rupture, endocarditis, or a chronic fibrosis of the segments. (*a*) Rupture of the valves or of the chordæ tendineæ may follow a blow on the chest or an excessive effort. (*b*) The endocarditic form occurs in the acute infections, more particularly rheumatic fever. (*c*) The etiology and appearance of fibrosis of the tricuspid valves are similar to those of the mitral.

Because of the lessened strain put upon the tricuspid valve in adult life, inflammation and degeneration of its leaflets are much less frequent than in the mitral valve. Probably also because of the greater tension which has to be borne during fetal life, the relative frequency of endocarditis in the right and left sides is reversed. Congenital endocarditis is almost always confined to the right side of the heart. In adult life affections of the tricuspid are rare. By far the most frequent cause is rheumatic fever, and when present on the right side, endocarditis is, in the majority of cases, associated with the same process of the mitral valve, of the aortic valve, or of both. In addition, affections of the valve

have been determined to be due to the pneumococcus, gonococcus, tubercle bacillus, streptococcus, and typhoid bacillus. Gummatous change of the valves has been described. As a sequence of other valvular disease, mitral or aortic, degenerative changes may cause insufficiency. Malignant disease is extremely rare.

2. Relative insufficiency arises in a large number of conditions. The fibrous ring which surrounds and supports the auriculoventricular orifice is liable to become stretched, and at the same time the muscle of the ventricle suffers distension. This means a larger orifice for the valves to close, and as the chordæ tendineæ cannot elongate, the orifice remains open, its cups not being able to meet in close apposition. It is a question whether the inability of the muscle to lessen the ventricular cavity to its normal size in systole does not play a large if not the chief part, for if at the height of systole the cavity were no larger, it is conceivable that, even with a dilated ring, no regurgitation might occur; but if with a dilated ventricle, the degree to which the ventricle can contract be lessened, then the cavity is fuller at the end of systolic than normal, and the valve cusps are not properly approximated.

The important part played by the muscle of the ventricle was put forward in a masterly way by T. Wilkinson King[1] in 1837, and the following account which he gives of the anatomical relations of the tricuspid valve and its connection needs no revision. "The right auriculoventricular opening is oval; and to its circumference, the membrane of the tricuspid valve has attachment, without any distinct interruption; whilst its floating border, depending into the ventricle, is deeply fissured, so as to form three or more scalloped or angular curtains. And it appears from careful examination that the united areas of these valvular portions are scarcely more than equal to the mean extent of the oval opening. One of these curtains (which, not being movable, I have called fixed) occupies the left margin of the aperture in apposition with the solid wall, from which arise all the cords that serve to secure the free edges and ventricular surface of the fixed curtain. These cords are of such a length as scarcely to allow the curtain to rise into the plane of the oval opening in the natural play of the valve, and being destitute of muscular columns, cannot by any possibility set the valve in motion, or serve any other purpose than that of preventing too great a reflex of the curtain itself. A second curtain (the anterior) is attached at the anterior and right edge of the opening, having one free border forward and another backward in the ventricle. Each border has its proper set of cords: the anterior, or upper, set having their insertion into a mere nipple of muscle on the solid wall, in the direction of the pulmonary artery; and the inferior, or posterior, are as invariably collected with numerous others into the summit of a muscular column, whose base is inserted into the thin right, or yielding wall, of the ventricle near its centre, where also is attached, almost as regularly, another muscular band which stretches across the cavity between the two walls. This band may have an average length of six or seven lines and a circumference of three or four. It seems

[1] Safety Valve Action in the Right Ventricle of the Human Heart, *Guy's Hospital Reports*, London, 1837, vol. ii, p. 104.

calculated to limit distension, and therefore I have called it the moderator band of distension. The third curtain or fold of the valve (the right) is situated on the right side of the aperture posteriorly, and has little or no connection with the inner or left edge of the opening. In extent and figure it varies considerably, and it rarely forms one single scallop, but is frequently fissured so as to form two or three, more or less complete. Its cords are accordingly arranged in two or more sets, the greater part of which are attached by the intervention of muscular columns to the outer yielding wall, at a considerable distance from the solid wall, and usually without any transverse bridge or moderator band.

"The construction . . . I have described in connection with the yielding, *i. e.*, the outer wall of the ventricle, constitutes the main peculiarity of arrangement and action in the tricuspid valve, the great extent, thinness, and feebleness of the yielding wall rendering it liable to the distending influence of venous accumulation in various degrees; the curtains being three, and each one tethered to that part of the ventricular parietes immediately beneath itself (but most extensively to the yielding wall), by the intervention of columns whose passive effect is to produce a retraction of the curtains in proportion to the distension, and whose active contractions serve, under dilatation, to augment the valvular retraction, or rather to maintain it at its height during the imperfect systole . . . and further, the orifice itself, depending on the yielding wall, may admit of some relaxation and thus assist to produce regurgitation."

Following these anatomical observations, King performed several experiments on human hearts in which no disease could be detected. By putting pressure into the left ventricle, it was easy to effect a complete and adequate closure of the mitral valve, and only with very considerable pressure did the escape of water into the auricle occur. In the right ventricle, however, no position of the heart and no variation of the conditions were sufficient to prevent the escape of a tape-like stream of water into the right auricle, unless the walls of the ventricle were at the same time compressed by the hand. King suggested the effect of cardiac tonicity on the production of a complete valvular ring, and demonstrated it by showing in a heart, in which rigor mortis appeared after removal, that the deficiency of the valve became almost negligible.

Relative tricuspid insufficiency, therefore, is really one caused by affections interfering with the muscle of the right ventricle, and its causes may be summarized as follows:

(*a*) Mechanical dilatation, due to an increase in pressure in the ventricle at the beginning of systole, may be caused by overexertion, asphyxia, and abnormal fixation of the chest wall, as in some forms of labor. Other causes are those which oppose an obstruction in the pulmonary circulation—chronic bronchitis, sclerosis of the lung arteries, bronchiectasis, chronic fibroid disease of the lungs and pleura, and disease of the mitral valve. The ease with which this dilatation is brought about may be shown by the fact that, by holding the breath for one minute, the right border of the heart, as determined by deep percussion, travels to the right at least an inch.

(*b*) Dilatation of the right ventricle, the result of a failure in muscular nutrition, is observed in all forms of local cardiac disease, myocarditis, pericarditis, and gummata of the heart. Of general diseases, the most important are malnutrition, as in diabetes, cachexia from neoplasms, debility from atonic conditions of the stomach, and in the anemias, especially in pernicious anemia. Prolonged and high fever tends to an enfeeblement of the cardiac muscle and to insufficiency of the tricuspid valve.

Pathological Physiology.—*Mutatis mutandis*, what has been said of mitral regurgitation applies here. With insufficiency, the first stress is thrown upon the right auricle, which, by hypertrophy and compensatory dilatation, opposes a mechanism against the effects of regurgitation. When the regurgitation becomes greater and the cavity of the auricle has to dilate to such an extent that it cannot exert sufficient force on the contained blood, the muscle bands by which the orifices of the veins are closed during systole are stretched and become ineffective. There is then during systole of the ventricle, a continuous column of liquid from the ventricle into the veins without the opposition of any valvular mechanism. It is obvious, then, that the condition of the blood in the venous system, from the clinical aspect, is of considerable importance. Mackenzie has shown, by tracings of this pulsation taken in numerous cases of heart disease, that when the right side of the heart is at fault, as in failure from mitral disease, a change often comes over the jugular pulse in which the auricular wave diminishes or disappears, and the ventricular wave increases in size and occurs earlier in relation to the ventricular output, than in normal cases.

FIG. 14

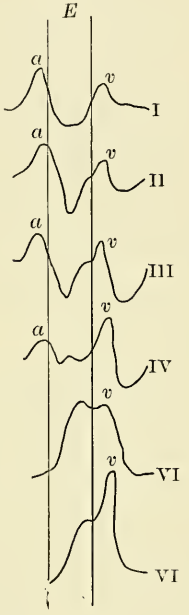


Diagram to show the transition from the normal venous pulse to the ventricular form, *i. e.*, in tricuspid insufficiency. *I*, is the normal venous pulse from which the *c* wave, occurring between *a* and *v*, probably due to the carotid artery, has been omitted; *a*, auricular wave; *v*, ventricular wave, whose significance in the normal venous pulse is doubtful. *E*, period of outflow into the pulmonary artery. (After Mackenzie.)

The transition is shown diagrammatically in Fig. 14. When the alteration is fully developed, there is only one large wave in the jugular pulse, which for the most part is ventricular in time. Mackenzie calls this form of venous pulse the "ventricular" form, and has taken it to mean tricuspid regurgitation. This view has recently received striking confirmation by Rihl,[1] who, by making an artificial lesion of the tricuspid valves in rabbits, finds that, according to the severity of the lesion, there are two sharply defined forms: first, that in which the regurgitation is slight and the venous pulse shows no change from the normal; and,

[1] *Verhandlungen des Congresses f. innere Medizin*, 1907.

secondly, that in which the venous pulse is of the ventricular form. We must suppose that in the former condition, the auricle of itself can compensate for the regurgitation, without undue stretching of its walls by the regurgitated blood. This is confirmed by finding that in these less severe forms, stimulation of the vagus, the beginning of asphyxia, and so on, which in the normal animal are without effect on the jugular pulse, in the mutilated animal, produce a ventricular venous pulse.

Morbid Anatomy.—The heart in pure tricuspid insufficiency has certain distinctive features. The right auricle is dilated and globular, the right ventricle is more prominent and fuller than normal, and appears to be creeping round the left ventricle. The amount of distension of the right auricle and ventricle depends on the rapidity of onset of the lesion, on whether organic disease is present in the valves, the condition of the muscular walls, and so on. The best example of a pure functional tricuspid insufficiency is to be seen in death from asphyxia, in which the right heart, especially the auricle, is enormously dilated. When organic disease of the valve is present, the ventricle and auricle have had time in part to oppose a certain amount of hypertrophy against the valvular defect, consequently in the organic cases the enlargement is not so great, and is made up of hypertrophied muscular wall, in addition to the dilated cavity.

The condition of the valve in relative or functional insufficiency is normal, the cusps being thin and the chordæ tendineæ not thickened or shortened. In the case of organic insufficiency, the state of the valve will vary according to the cause. The valve may have been ruptured, either by effort or by a blow. A recent endocarditis takes the form of small excrescences, or larger irregular masses, attached to the valves. If, on the other hand, there is chronic fibrosis, the cusps are thickened, glistening white or yellowish, and the chordæ tendineæ thickened and shortened. The mural endocardium in the chronically dilated cavity is always thicker than normal. On account of the pressure to which they have been subjected, the veins opening into the right auricle are dilated, their walls are slightly thicker than normal, and this thickening extends into the jugular and the subhepatic veins.

The liver, spleen, and kidneys all show the chronic cardiac congestion described under mitral disease; in fact, these appearances in the two diseases are due to failure of the right side of the heart. The lungs in experimental animals are dry and bloodless, and the same has been noted in pure cases of tricuspid insufficiency in man.

Symptoms.—The chief complaint of the patient is breathlessness on exertion, and if the lesion is uncompensated, there is quickened breathing or orthopnœa, even at rest. The slightest exertion causes dyspnœa and a sudden sense of oppression in the chest. In advanced cases orthopnœa is marked. Pain is not a prominent symptom. It most frequently occurs in relation with an enlarged liver whose capsule is stretched, and consequently the pain is felt on the right side of the abdomen. The digestion is always faulty and the appetite is lessened or absent. Distension of the abdomen, either in relation to meals or not, is common, relieved sometimes by eructations or by purgatives. Œdema of the legs and

feet sets in early and is of the usual type, being less evident after a night's rest in bed. Ascites may be present even before any œdema occurs.

Physical Signs.—The facies of the patient with marked regurgitation is one of intense cyanosis. The whole surface of the skin is a livid blue color, the extremities, such as the ears, the tip of the nose, and the fingers being of a deeper color than the rest of the skin. The lips are a violet blue. The sclerotics are darker than normal and of a subicteric tint. The visible veins, such as those of the temple, neck, arms, and chest, are dilated and prominent. If noticed carefully, two types of pulsation may be distinguished in those of the neck: first, rhythmical emptying and filling; secondly, pulsations synchronous with the heart beats, best seen in the right supraclavicular triangle outside the sternomastoid, over the spot where the external and internal jugular veins enter into the subclavian. In fact, the jugular sinus may be so dilated as to form a rounded swelling just above the clavicle. The pulsations may extend over the veins of the shoulders and mammary regions and down the superficial veins of the arm and the elbow. Inspection may show a large area of precordial pulsation, especially noticed over the lower end of the sternum and in the epigastrium. In cases with a marked pulsation in the jugular veins, pulsation in the liver can usually be both felt and mechanically recorded.

The apex beat is diffuse and extends outward to the left as far as the nipple line or farther into the left axilla. On palpation, sometimes a light systolic shock may be perceived. On determining the limits of pulsation, the area is found to lie over the lower end of the sternum and along a strip stretching from the sternum to the apex beat, an area corresponding to the right ventricle. On percussion, the transverse dulness is increased and stretches more to the right than normal. Schwartz has recently suggested that the deep cardiac dulness in relative tricuspid insufficiency extends farther to the right than in organic deficiency of the valve, and he suggests that dulness extending beyond three fingers' breadth to the right of the sternum—it sometimes extends as far out as the right nipple line—should be regarded as almost certainly due to relative tricuspid insufficiency; because the stretching of the ventricular muscle must be great in order to produce insufficiency.

On auscultation a *systolic murmur* can usually be detected in the cardiac area. It may be rough, especially if the insufficiency is the result of endocarditis. On the other hand, if the insufficiency is relative, it is faint and delicate. Tricuspid systolic murmurs are more superficial than mitral; their pitch is higher and their duration longer. Tricuspid murmurs are accentuated if the patient is lying flat on his back with the head strongly extended backward. The point of maximum intensity is over the sternum and to the left rather than to the right. It may, however, be heard to the right of the sternum, which can hardly ever be done in mitral insufficiency.[1] The *x*-rays, as has been pointed out by Bonninger,[2] may be used as a means of distinguishing certain heart lesions. In a case of pure tricuspid insufficiency, the maximum pulsation

[1] Heitler, *Deutsch. med. Woch.*, 1897, p. 106.
[2] *Deutsch. med. Woch.*, 1907, p. 333.

is toward the right border of the heart, and the extended pulsation of the left auricular region, so characteristic of mitral failure, is absent.

Diagnosis.—From a careful observation of the jugular pulsation in the neck, and careful auscultation over the precordia, there is seldom much doubt as to the presence or absence of tricuspid regurgitation. The veins of the neck show, in proportion to the deficiency of the valve, a pulsation which is synchronous with the ventricular systole. If, by observation, the time of the most prominent wave is not easy to determine, then a tracing of the pulsation, especially if combined with an apex tracing, will determine exactly the time of the jugular pulsation. To distinguish the murmur of mitral regurgitation from that of tricuspid regurgitation is by no means always easy. Mitral systolic murmurs may be loudest at almost any point to the left of the sternal border, below the second interspace; less frequently they have their maximum intensity over the ensiform process. The tricuspid murmurs are soft, blowing, rarely rough, more superficial, shorter, and usually higher in pitch. The loudest can be heard over the entire sternal area, generally plainest opposite the fourth interspace, and more distinct over the middle and left half than toward the right side of the sternum. Less frequently they are heard best over the lower half of the sternum. The conduction of the murmur may be either to the right or to the left, to the left better than to the right. Faint murmurs are not heard above the third rib.

It is important to determine whether the incompetence is relative, due to stretching, or from organic change in the valves. The following points are suggested by Schwartz:[1] With a positive venous pulse and a percussion dulness of the right border of the heart not extending beyond three fingers' breadth to the right of the right sternal edge, an organic lesion of the tricuspid is the more probable. If, on the other hand, the right cardiac dulness extends farther to the right than three fingers' breath, a relative insufficiency is more probable, because the valves are insufficient by the stretching of the muscle, which may be so great as to make the right border extend by percussion to the right mammillary line. In organic insufficiency after the reëstablishment of compensation, the positive venous pulse remains, while in relative insufficiency, the positive venous pulse is replaced by one in which the auricular wave becomes more prominent.

Prognosis.—In those cases in which the deficiency is due to organic disease, the prognosis is always grave, for only very rarely is it unaccompanied by disease elsewhere in the heart and because any failure of the right ventricle is immediately followed by symptoms of heart failure. In relative tricuspid insufficiency, the prognosis depends more on that of the cause of the insufficiency than on the valvular defect itself.

TRICUSPID STENOSIS.

Etiology.—Tricuspid stenosis may follow an infective process or be the result of a primary degeneration of the tissue. The character of the

[1] *Verein f. innere Medizin*, Abstract in *Deutsch. med. Woch.*, 1903, vol. v, p. 318.

infection is often doubtful, and we are therefore driven to examine clinical, in conjunction with postmortem, records. Leudet, in 1888, collected a series of 114 cases. Herrick, in 1897, added 40 cases. Newton Pitt, in 1899, collected from the records of Guy's Hospital a total of 87 cases out of 12,000 postmortem examinations, and Wardrop Griffith, in 1903, studied 19 cases from the postmortem records of the Leeds Infirmary and the specimens in Yorkshire College Museum. In a majority of cases, rheumatic fever was the most important single factor. In the 173 cases of Leudet, Herrick, and Griffith, 59 had a definite history of rheumatism or chorea, *i. e.*, 34.9 per cent. In Newton Pitt's series, the percentage is much greater, 62.06 per cent.; and if the cases with a history of vague rheumatic pains be admitted, the proportion becomes somewhat larger. Of other infections causing tricuspid stenosis we have no certain knowledge. Syphilis is mentioned as an antecedent in one of Griffith's cases. Two cases have been reported in which a pedunculated ball-like tumor projected down from the auricle and partially occluded the tricuspid valve.

Females are affected much more frequently than males; in a total of 260 cases collected by Leudet, Herrick, Pitt, and Griffith, 179 were females, 63 were males, and in 15 the sex was not mentioned. The age incidence at death is well shown from Pitt's series of cases: between eleven and twenty years, 16 cases; between twenty-one and thirty years, 31 cases; between thirty-one and forty years, 22 cases; between forty-one and fifty years, 10 cases; between fifty-one and sixty years, 3 cases; between sixty-one and seventy years, 2 cases.

The association of other cardiac lesions is a special feature in tricuspid stenosis; thus, in the 173 cases collected by Leudet, Herrick, and Griffith, the following valvular lesions were found: stenosis of the tricuspid valve alone in 12 cases; stenosis of the tricuspid valve with mitral stenosis in 97 cases; with pulmonary stenosis in 3 cases, with lesions of the aortic and mitral valves in 58 cases, and with lesions of the mitral and pulmonary valves in 3 cases.

Pathological Physiology.—A pure stenosis, gradually increasing in degree, causes an overfilling of the right auricle, and by stretching the muscle of the auricular wall, this leads to more vigorous contractions and is followed by hypertrophy of its muscular wall. As the stenosis increases, the auricle, even although hypertrophied, will not be able to empty its contents during systole, and consequently the cavity enlarges. The closure of the veins which open into the right auricle is probably effected by the muscular bands, especially those which lie around the venous openings. In the dilated auricle these are unable to contract properly and the veins remain open. Consequently, at each auricular systole a regurgitant wave, presystolic in time, travels up and distends the vein. The hypertrophy causes a greater wave than normal. With increase in the stenosis, the auricle tends to become so dilated that its power, even although hypertrophied, is inadequate to expel more than a fraction of the blood into the ventricle. The auricular pulsation then fails, and with it the transmitted pulsation in the jugular veins. These two conditions correspond to two types observed clinically: first, the

cases in which there is jugular pulsation in turgid veins, auricular in time; secondly, the cases in which, although the veins are turgid, no pulsation can be observed in them.

Morbid Anatomy.—The general appearance of the body is the same as that in death from chronic mitral disease with anasarca. The cyanotic tint is more marked than in other cardiac lesions. As tricuspid stenosis is so often associated with mitral stenosis, it is not always easy to say which anatomical features correspond purely to the former. If the heart be stuffed before being opened, the chief feature is a marked enlargement of the right auricle associated with a dilatation and a thickening of the walls of the superior vena cava and its branches. This dilatation may be sufficient to do away completely with the function of the valves, so that there is a continuous cavity from the venous system to the right auricle. This is well shown in one recorded case in which there was a continuous clot extending from the right auricle into the veins of the neck. The state of the right auricle depends upon the conditions of the circulation at the time of death; if this has occurred while the auricle by hypertrophic increase has been capable of propelling blood through the constricted orifice, the cavity of the auricle is large and its walls thickened by more layers of muscle fibres. But if the patient has lived a stage farther, the cavity is dilated and the wall of the auricle very much thinned, so much so, that in areas as much as 5 cm. across, the auricular wall is composed of epicardium and endocardium alone. The rest of the muscular tissue of the auricle is proportionately thinned in these cases. The endocardium of the auricle, in consequence of continued back pressure, undergoes increasing thickening, and at death is much less transparent than in a normal right auricle. The tricuspid orifice is narrowed in different cases, to different degrees; cases have been reported in which it scarcely admitted the little finger. The three cusps are so welded together and thickened that they are indistinguishable, except by comparison with their relations to the papillary muscles. The chordæ tendineæ are thickened and shortened. Other appearances have been described. In the case reported by Gairdner the orifice was blocked by a fibrinous ball attached to a point on the auricular wall. In another case reported by Philip,[1] large recent vegetations filled up the cavity. The right ventricle showed some enlargement of its cavity and thickening of its walls. In almost all accurately recorded cases some degree of mitral stenosis has been present.

The condition of the lungs varies, and in this regard also we cannot distinguish the effects of a tricuspid stenosis from those of a mitral stenosis. They are sometimes found to be dry on section, with only a small amount of hypostatic congestion at the bases and no marked œdema, sometimes markedly œdematous and congested with pneumonic consolidation at the bases, or with hemorrhagic infarcts. The liver, although presenting the appearance of chronic stasis, is not always enlarged; in fact, some livers have been distinctly below the average size (Stow's case). The edges are rounded, as would be expected from

[1] *Edinburgh Hospital Reports*, 1893, vol. i, p. 235.

the chronic overfilling with blood under pulsation; the capsule is thickened, and on section, the organ drips with very dark blood, showing a surface with the features of the "nutmeg" liver. A notable feature is the increase in connective tissue. Perihepatitis has been observed.

Symptoms.—That a considerable degree of stenosis may not be productive of symptoms is shown by the history, reported by Gairdner, of a man who was under observation for ten years, led an active life, and died at the end of the period from pneumonia. The symptoms of tricuspid stenosis are in the main very similar to those of tricuspid insufficiency, but they present certain important differences. Cyanosis may be present for a year, or even longer, before any other sign of cardiac failure. It is not of a very pronounced grade, nor so marked as that seen in extreme degrees of congenital heart disease, but is often sufficient to give trouble to the patient and to give occasion to remarks. Breathlessness is the most frequent complaint; it is more marked and comes on sooner than in lesions of the left side of the heart. Even very slight exertion, such as walking, may bring on severe dyspnœa. Other symptoms of heart failure differ in no respect from those in left-sided lesions, such as œdema, ascites, pain in the right hypochondrium from the engorged liver, indigestion, constipation, and so forth. In certain cases anginal pain is complained of, which may pass down the left arm, occasionally down the right. It is often questionable in a given case which symptoms are due to the tricuspid stenosis and which to the frequently associated mitral stenosis. Gairdner's patient complained of the jugular pulsation in the neck. All patients in whom the cyanosis is marked, complain of great susceptibility to cold. Hemoptysis, noticed in twenty cases in Newton Pitt's series, is probably due to the mitral stenosis.

Physical Signs.—The patient, as a rule, is cyanotic, the tint being most marked in the lips, nose, ears, and hands. The veins are dilated and may be specially noticed in the lower part of the neck. The jugular bulb may be dilated to such an extent as to produce an ovoid swelling, which may or may not show pulsation. If none is visible, it may often be brought out by getting the patient to sit or stand up. An important distinction between stenosis and insufficiency of the tricuspid valve lies in the form of the jugular pulsation; in the latter, the type of the jugular pulse is ventricular, *i. e.*, the most prominent wave is systolic in time; in tricuspid stenosis the largest wave is the auricular, and hence presystolic. Mackenzie has pointed out this distinction, and, further, that the liver pulsation, which is a constant feature of these cases, shows a large wave, also auricular in time. The narrowing of the tricuspid orifice protects the auricle from the overdistension due to a large regurgitant stream, while the overfilling of the chamber, from a diminished outflow through the contracted orifice, serves to stimulate the auricular muscle to vigorous action and hypertrophy. The auricular pressure forced into the veins in systole often causes so great a tension in the valves at the entrance of the internal jugular vein that an audible sound, auricular in time, is heard on auscultation over this area. When fulness without any pulsation is present, there is probably a paralysis of the right auricle from overdistension.

Inspection.—As, almost without exception, there is associated mitral stenosis, it is difficult to separate the signs due to tricuspid stenosis alone. The area of pulsation is greater than normal, the apex is usually localized with difficulty and is seen farther out to the left. Some pulsation is seen in the costosternal angle.

Palpation.—A thrill presystolic, sometimes systolic, in time can be felt, the presystolic having its maximum intensity over the lower end of the sternum.

Percussion.—The cardiac dulness is increased to the right and occasionally in the upward direction.

Auscultation.—In the majority of cases recorded there has been a rough presystolic murmur, not quite so harsh as that heard in mitral stenosis. The point of maximum intensity and its area of audibility differ in different cases, but it may be said generally that the maximum point is somewhere near the lower half of the sternum, and it is propagated radially from that point. Sometimes it is heard over the entire sternum, more distinctly to the left side, sometimes over the lower half of the bone. Occasionally the murmur is heard to the right. Polycythemia is almost constant, and, as a rule, well marked, often 8,000,000 or 9,000,000 red cells per cubic millimeter. The fingers are frequently clubbed. If there is any cardiac failure, the urine contains albumin, and glycosuria has on rare occasions been noticed.

Diagnosis.—The reports of a large number of cases show that tricuspid stenosis may be mistaken for mitral stenosis, for tricuspid insufficiency, for congenital cyanosis, for pulmonary stenosis or deficiency of the septum of the auricles.

Considering the similarity of the symptoms in mitral and tricuspid stenosis, it is not surprising that the rarer lesion is occasionally overlooked. The points of distinction are as follows: The cyanosis in tricuspid stenosis is more marked and more constant; in mitral stenosis the cyanosis is more clearly associated with a loss of compensation and with stasis in the pulmonary vessels. If digitalis be given to a patient with mitral stenosis, the cyanosis, as a rule, lessens, but in a patient with tricuspid stenosis little, if any, effect can be noticed. A careful examination of the chest and neck should be made, and attention paid to the following points: If the veins of the neck are full and pulsate with each auricular beat, tricuspid stenosis is more likely. In mitral stenosis with cardiac failure, insufficiency of the tricuspid would be produced and a positive, *i. e.*, systolic, *i. e.*, ventricular, venous pulsation would be produced. The precordia should be carefully palpated to determine the delimitations of any thrill that may be present. A presystolic thrill in the neighborhood of the apex suggests a mitral lesion; one more to the right, especially if its point of maximum intensity be felt on or near the sternum, suggests tricuspid stenosis. Careful auscultation, again, will sometimes show that a presystolic murmur present at the apex, alters its character on being traced to the right, toward the sternum, and with its altered character becomes more intense in that region. In a case recorded by Mackenzie the presystolic murmur produced at the tricuspid orifice could be heard over the whole of the lower two-thirds of the sternum and over a considerable area to the right.

Several cases are on record in which physicians of great experience have mistaken a tricuspid stenosis for insufficiency, even although repeated examination has been made for signs of tricuspid stenosis. It is well recognized clinically that mitral stenosis with loss of compensation may be, at times, difficult to recognize. This is also probably true of tricuspid stenosis. The mitral stenosis, in the stage of loss of compensation, is mistaken for mitral regurgitation; similarly the tricuspid stenosis, with loss of compensation, is mistaken for one of tricuspid regurgitation. To follow this a little farther, reference has been made, in speaking of mitral stenosis, to the work of Mackenzie and his suggestion that the disappearance of the presystolic mitral murmur is associated with the assumption of a disorderly rhythm and the disappearance of the auricular wave in the venous pulse. Mackenzie considers that the disorderly heart rhythm is due to the stretching of the primitive muscle tissue, increasing its excitability and causing it to act as the stimulus to the ventricular muscle instead of the normal impulse from the superior vena cava. An examination of the records showed that although in many cases a venous pulse has been noticed, recorded graphically, and proved to have an auricular wave, in others no pulsation of the veins of the neck has been seen. Cases, however, which have shown an auricular venous pulse have also had a regular pulse rhythm, a presystolic thrill, and murmur in some situation, which suggest a tricuspid rather than a mitral origin. It is suggested, then, that in those cases in which competent observers have diagnosed tricuspid regurgitation, insufficiency alone was indicated; the symptoms of stenosis having disappeared by reason of the failure of the auricular contractions.

Prognosis.—The gravity of stenosis of the tricuspid valve depends on its association with mitral stenosis in a great number of cases. Mackenzie supposes that tricuspid stenosis is a lesion which protects the rest of the heart from the ill effects of overfilling. This view is borne out by what was noticed in Gairdner's patient, who led the life of a laborer for many years without any obvious symptoms. When mitral stenosis is present at the same time, the additional lesion means a much greater strain on the cardiac mechanism, and the length of life in such cases would be in proportion to the gravity of the lesion on the left side of the heart. In Newton Pitt's series of 87 cases, 31 died between twenty and thirty years of age, the others in a lessening proportion in the previous and succeeding age decades.

PULMONARY INSUFFICIENCY.

From the clinical stand-point, so much that has been said about pulmonary regurgitation is either unproved or as yet incapable of proof that the subject should be approached with the greatest caution, and with as clear as possible a conception of the theoretical aspects.

Structurally, the pulmonary valve and its surroundings differ from those of the aortic valve in their more delicate texture, and in the adult the segments do not, as a rule, show the medial thickening about the corpora Arantii. The wall of the pulmonary artery is thinner than that

of the aorta and has not the same tendency to preserve its ring structure in the absence of an internal pressure. The conus arteriosus which leads into the pulmonary is more thin-walled than the corresponding part of the left ventricle, and under increased internal pressure is probably capable of considerable dilatation. The structures in relation to the pulmonary valve are obviously directed as a whole to withstanding much less pressure than the corresponding parts of the aorta, and this is borne out by what is known regarding the relative pressures in the two sides of the heart.

G. A. Gibson showed that in the pulmonary artery of the sheep, pressures above 14½ inches caused a strong jet of water to escape through the pulmonary valve into the ventricle; with less than this, and down to a pressure of 9 inches of water, there was a small escape; below 9 inches the valves were competent. In the healthy human heart much fluid escaped with a pressure above 13 inches, a small amount between 13 and 8 inches, and none below that pressure. We have no direct means of estimating the pressure in man. The results of animal experiments give as the mean pressure 17.6 mm. of mercury in the cat, 12.07 mm. in the rabbit, and 29.6 mm. in the dog (Bentner). Eight inches of water is equal to about 15 mm. of mercury, so that the pressure in the pulmonary artery in man at the height of a vigorous systole of the right ventricle may cause a pressure well above that which first begins to cause insufficiency.

Etiology.—Insufficiency of the pulmonary valve may be caused by an acute endocarditis, by chronic fibrosis of the segments, or by dilatation of the orifice at the site of their attachment. Insufficiency from acute endocarditis is seen in gonorrhœa, rheumatic fever, pneumonia, scarlet fever, pyemia, and puerperal fever. It is remarkable that in the cases collected by Newton Pitt, from the records of Guy's Hospital, nearly half those in which a definite infective cause was ascertained were due to the gonococcus. An interesting form is associated with aneurism of the aorta (Newton Pitt), in which an inflammatory change in the neighborhood extends to the pulmonary artery and causes an adhesion of one or more cusps of the pulmonary valve to it. Sclerosis of the leaflets is met with in long-standing cases of mitral disease, sometimes in emphysema and chronic affection of the lungs. Rupture and deficiency in the number of the valves are rare causes of insufficiency.

Relative pulmonary insufficiency may follow long-standing obstruction in the pulmonary circulation. Our knowledge of these conditions is very scanty, but those which are most certain are left-sided valvular disease, especially mitral stenosis (Graham Steell), and general pleuritic adhesions (Rokitansky).

Morbid Anatomy.—In certain cases of infective endocarditis the orifice of the pulmonary artery may be narrowed by the vegetations. The right ventricle is enlarged to a degree depending on the duration of the insufficiency. The pulmonary artery may show patches of atheroma, especially if the insufficiency has been due to an obstruction in the pulmonary circulation, as, for instance, in mitral stenosis. It by no means follows that with evidence of pulmonary regurgitation during

life this can be demonstrated postmortem; it depends wholly upon whether the elastic tissue of the base of the pulmonary aorta has been damaged. The ordinary methods of testing the efficiency of the valve postmortem, namely, by pouring water into the artery in the excised heart or measuring the diameter of the pulmonary orifice, only give the efficiency in the collapsed state of the organ, and not when it is distended by blood. This is probably the reason why, in mitral stenosis, it is often possible to detect a diastolic murmur down the left of the sternum and yet seldom is it possible to find evidence of regurgitation postmortem.

The other organs, in death from cardiac failure in this condition, differ in no respects from "cardiac" organs in other conditions.

Symptoms.—Only when failure of the right ventricle is present, do symptoms appear, cyanosis, dyspnœa, œdema, failure of appetite, etc. Epistaxis has been recorded in some of the cases, and in one case (Oliver's, 1907) it caused death. Hemoptysis from emboli in the lungs is frequent in infective cases. A third group of cases are those in which the signs of an infective process, such as puerperal septicemia, are the most noticeable, and, unless special attention be directed to the heart, are frequently not diagnosed during life.

Physical Signs.—The precordial area of pulsation is enlarged, the apex beat is to the left of the nipple line, diffuse epigastric pulsation is visible, and frequently pulsation to the left of the sternum in the second and third interspaces and jugular pulsation are present. The cardiac dulness is increased transversely. The auscultatory signs are the most important and those upon which alone a diagnosis can be made. The murmur of pulmonary regurgitation, as a rule, is coarser than that in aortic regurgitation, often grating, and more superficial. It is heard best down the left side of the sternum, and is propagated not along the systemic arteries, but along the left pulmonary artery. The second sound at the aortic area can usually be well heard, somewhat higher in pitch than that at the pulmonary valve, if present. It is often possible to detect pulsation in the lung vessels from the rhythmic constriction of the pulmonary alveoli; the vesicular murmur is rendered louder during ventricular systole.

Diagnosis.—In the case of pulmonary regurgitation, this is at all times difficult; the following points require special attention: (*a*) The character and situation of the murmur, its presence down the left side of the sternum and the rougher quality than that produced at the aortic valve. (*b*) The character of the pulse; Corrigan's pulse being invariably absent in pulmonary artery disease, though it should be remembered that Corrigan's pulse is not invariably present in aortic regurgitation. (*c*) The murmur of pulmonary regurgitation is increased in intensity during expiration or in expiration with a closed glottis (Valsalva's experiment). (*d*) The character of the apex beat, which in right-sided valvular disease is diffuse and displaced downward and outward.

Prognosis.—In the acute cases, the outlook depends on the cause of the endocarditis. The streptococcus, gonococcus, and pneumococcus cases are usually fatal. In the more chronic forms, some time is allowed for hypertrophy of the right ventricle, and not until this fails will there

be signs of circulatory insufficiency. In relative insufficiency also a line of defence is present in the hypertrophy of the right ventricle; but the prognosis is associated rather with the original cause of the disease than with the pulmonary regurgitation.

PULMONARY STENOSIS.

This is an exceedingly rare, acquired lesion. The congenital form is discussed elsewhere, and only the acquired form is considered here.

Etiology.—The causes are much the same as have been described in the section on aortic stenosis. (*a*) Endocarditis is the most common cause, and may occur in the course of rheumatic fever, or one of the other acute infections. In some instances the vegetations are very large. (*b*) Chronic sclerotic changes may occur as at the aortic orifice, sometimes associated with endarteritis of the pulmonary artery. (*c*) Rare instances due to trauma have been recorded.

Morbid Anatomy.—The changes are much like those at the aortic orifice. In the form with endocarditis, the vegetations may be very large, and almost block the orifice. In some cases the process may be more in the conus arteriosus, and this is often due to endocarditis of the ventricular wall. In the sclerotic form the cusps are thickened, and may be adherent, forming a much narrowed orifice. Calcareous deposits may form, so that the orifice is nothing but a rigid ring, in which case the stenosis is accompanied by regurgitation.

Pathological Physiology.—Practically the same changes arise, as are found in the left heart in aortic stenosis. In pure stenosis, hypertrophy of the right ventricle is the most marked early change, as by this compensation is maintained; but, when insufficiency is combined, dilatation and hypertrophy result. With marked stenosis there must be some decrease in the pulmonary circulation. As the right ventricle fails, tricuspid insufficiency will appear.

Symptoms.—As long as the lesion is well compensated, these will be few. There may be some shortness of breath on exertion, but this is usually not marked. The same may be said of œdema and the symptoms due to venous engorgement. With loss of compensation, dyspnœa and cyanosis may both be marked, and œdema of the legs and the symptoms of passive congestion appear.

Physical Signs.—On *inspection*, the apex beat may be somewhat out to the left, and there may be quite marked heaving pulsation over the lower sternum and adjoining left costal margin, as well as in the epigastrium. If there is loss of compensation, the veins in the neck are full, and show pulsation, as described under tricuspid insufficiency. On *palpation*, a systolic thrill is usually felt at the base, sometimes over rather a wide area, or especially marked in the second left interspace. On *percussion*, the area of dulness is increased to the right. The most important signs are obtained on *auscultation*. A systolic murmur is heard, usually with its maximum in the second left interspace close to the sternum. It is sometimes propagated upward and to the left. The murmur is generally very harsh, often extends throughout systole, and

seems more superficial and closer to the ear than that of aortic stenosis. It may be heard over a considerable part of the chest, but is not transmitted to the vessels in the neck. In some instances the murmur has been described as being soft. The pulmonic second sound is usually absent, or very faintly heard. A diastolic murmur is present if there be pulmonic insufficiency. The pulse does not necessarily show any change until loss of compensation occurs, when it is small, weak, and sometimes irregular. Clubbing of the fingers is sometimes present.

Diagnosis.—In this the great rarity of the lesion must be kept in mind, and it should always be the last to be considered; every other possibility should be gone over before this lesion is diagnosed, and even then it is safe still to have doubts. The murmur of aortic stenosis may cause error, but the fact of the murmur of that lesion being transmitted to vessels of the neck is important. The pulmonary second sound is usually present in aortic stenosis and absent in pulmonary stenosis. The character of the pulse may aid, that of aortic stenosis being suggestive. Certain congenital lesions may give difficulty, especially a patent ductus arteriosus, in which the murmur is often longer, and persists after the second sound.

Perhaps the most common error is to make the diagnosis on nothing but the presence of a systolic murmur in the pulmonic area. To keep in mind how frequently a systolic murmur is heard there without any valvular disease, is to lessen the chance of the error. Among these conditions of occurrence are (*a*) anemia, (*b*) peculiarities in the relation of the lung to the heart, (*c*) in many healthy young individuals, especially after exertion, in whom its occurrence may be difficult of explanation. In all of these the murmur is usually variable and altered, especially by change in position and respiration. The other signs of organic disease are wanting. Occasionally the murmur of mitral insufficiency is heard high up on the left side of the sternum, and may give difficulty. The other signs, and especially the accentuated second pulmonic sound, are of aid in recognizing this.

Prognosis.—This is grave, as a rule, although the rarity of the lesion does not allow of much deduction from experience. The condition of the right ventricle is most important. With any signs of its failing, the outlook is serious. One danger is the liability to pulmonary tuberculosis.

COMBINED VALVE LESIONS.

In nearly 50 per cent. of all cases the valve lesions are associated, either as a sequence, or two or more valves are affected at the same time. In the series of 1914 cases of valvular disease in the Edinburgh report, there were 230 with a double aortic lesion, 231 with a double mitral lesion, and 362 with various combinations of aortic and mitral lesions.

The same cause may act on two valves; thus, it is common in rheumatic fever in childhood to have the aortic and mitral segments attacked at the same time. Sclerosis may attack the aortic and mitral segments simultaneously. Occasionally an acute endocarditis involves the tricuspid

as well as the aortic and mitral, and in a few rare instances all four valves are found affected. A common association is insufficiency of the mitral valves as a sequence of lesion of the aortic segments. This relative insufficiency occurs so soon as the dilatation of the ventricle reaches a certain grade. In long-standing cases the tricuspid valves also become insufficient, and this is also a common sequence of stenosis and insufficiency of the mitral valves. Insufficiency of the pulmonary valves may also be combined with chronic lesions of the mitral. In consequence of the heightened pressure behind the chronic mitral lesion, sclerosis of the tricuspid segments may follow, with adhesion and gradual narrowing. The actual lesion of the valve is rarely pure stenosis or pure insufficiency. In the auriculoventricular orifices in particular, some degree of narrowing is usually present with the insufficiency. At the aortic orifices pure insufficiency of the arteriosclerotic type is comparatively frequent.

In connection with combined lesions, one or two cardiac axioms are to be remembered. The rheumatic heart in children is very apt to have both valves on the left side involved. In adults, particularly in women, the lesion of the mitral is often single. In men aortic insufficiency may be the only lesion, to be followed as the heart enlarges by relative mitral insufficiency. Combined aortic stenosis and mitral insufficiency occur in a few cases of rheumatic endocarditis in young persons, and in later life is sometimes a consequence of chronic sclerotic changes.

As it is chiefly by the character of the murmurs that we estimate these combinations of valvular defect, it may be well here to speak of their indications. A diastolic murmur heard over the body of the heart with a direction of propagation down the sternum indicates insufficiency of the aortic segments. In a few rare instances insufficiency of the pulmonary valves is present. The murmurs produced during diastole at the auriculoventricular orifice have special characters and qualities. A pure systolic murmur heard anywhere over the body of the heart does not necessarily indicate a lesion of a valve. So numerous are the conditions under which it may occur that the single systolic bruit heard anywhere over the heart is of no moment as an indication of valve lesion. It must always be judged of in conjunction with other features. In any case the position of maximum intensity of the murmur, the direction of the transmission, the existence of hypertrophy of the heart, or of one special chamber, must be taken into consideration. Combined diastolic and systolic murmurs give a more definite indication of lesion of a valve. Heard at the base in an adult, we may be reasonably certain that the aortic segments are involved. Heard at the apex region, the indication of mitral valve lesion is not so definite. In a case of pure aortic insufficiency, the systolic murmur at the base may be caused by slight roughening of the segments or of the intima of the aorta, while at the dilated mitral orifice there may be a loud systolic and a rough rumbling presystolic (Flint murmur), and both associated with relative insufficiency. In such a case a single valve lesion is responsible for four heart murmurs. In general, it may be said that the diagnosis of combined valve lesions from murmurs alone is not very satisfactory. Much more important

data are to be had from the study of the state of the individual chambers and the knowledge of the general cardiac pathology. In a child with an enlarged heart and a double murmur at apex and base, we are safe in diagnosing combined aortic and mitral valve lesion. In an adult man who has not had rheumatic fever, a similar combination may be produced by aortic insufficiency alone. Both in women and men mitral stenosis alone, or with insufficiency, may be the only lesion; but in cases of very long standing the valves on the right side of the heart are almost certain to be involved. As a rule, the physician is in a safer position if he limits his diagnostic ambition to two valves. Clinically, when lesions of three or four valves are determined with accuracy, mortifying postmortem disclosures are not unlikely to follow.

PROPHYLAXIS OF VALVE DISEASE.

That the profession as a whole scarcely appreciates the importance of preventive measures in disease of the heart is due in part to the fact that full knowledge is not yet available, and in part to the difficulty in making efficient what we already have. There died of disease of the circulatory system in England and Wales in 1905, 2716 persons under fifteen years of age. If we exclude from this list the congenital cases, we may say that a large proportion of the remainder should come within the category of preventable disease. In four directions we may work toward the lessening of the incidence of heart disease: (1) In the all-important endocarditic group of the acute infections, rheumatic fever plays the important rôle, and we need a more careful investigation into the conditions under which this disease prevails. Two circumstances appear to favor it. The damp, unsanitary surroundings of the poor seem to be the factor in the chronic tonsillitis and pharyngitis to which so many children are subject. More and more the profession has come to the belief that the portal of entrance of the germs of rheumatic fever is the tonsils and adjacent pharyngeal tissues. Careful attention should be paid to the state of the nose and throat. A mouth-breathing child should be regarded always as an unhealthy child, and enlarged tonsils and adenoids should be removed. Damp houses should be regarded as unsanitary. Wet cellars and wet walls favor the conditions under which rheumatic fever prevails. There is no single problem of greater importance in preventive medicine than the reduction of the enormous waste of life in children in consequence of the rheumatic infection. (2) In a second group the cardiac breakdown follows overuse of the muscles. This is most often a myocardial affair, but in a considerable proportion of cases there is disease of the valve. In the large public schools, boys should be carefully examined before they are allowed to enter into running and rowing contests. In a growing heart, the developmental energies of which are taxed to the uttermost between the ages of fourteen and sixteen, it must be most hazardous to throw upon it the extra burden of providing a work hypertrophy. No matter how careful the training, no boy of fifteen runs a mile race without serious risk. Both in schools and colleges much more stringent supervision should be exercised in

the matter of athletics. In the occupations, heart disease has become less common. With the introduction of machinery and the use of the lift in the mines, the liability to strain of the heart has lessened. (3) Syphilis, as a cause of heart and arterial disease, plays a very important rôle, and if we could ensure an early and more systemic and prolonged treatment of all cases much would be done to lessen the liability to myocardial and valvular lesions, and especially to mesaortitis and aneurism. In the army and navy, more particularly, these preventive measures may be of service. Even in the community at large the proportion of individuals who have had syphilis is very large, and we all know the difficulty in ensuring proper treatment. (4) And lastly, all circumstances which lead to arteriosclerosis promote the sclerotic type of valve lesion. Hard work, alcohol, and overeating, particularly when combined with the high-pressure life, are very apt to lead to early degenerations.

Much may be done to promote the establishment of compensation and to postpone the final breakdown. In a rheumatic case with endocarditis it is to be remembered that it is not simply the vegetations, but the proliferative changes in the substance of the valve that have to be considered. The quiet life without strain and without special effort will enable a valve to heal with a minimum of damage. With the development of incompetency, it may take months before the heart adjusts itself by hypertrophy to the new conditions. And the patient should be made clearly to understand the situation. It is always better to have a frank talk and explain the state of the "machine." Let it be expressed in mechanical terms, and make him understand that the difference between a healthy engine and his own is that in the former, for the ordinary purposes of life, only 25 per cent., say, of the horsepower is used, and there is a reserve of 75 per cent. to be called upon; whereas in his heart just the reverse conditions prevail, and while he may be perfectly comfortable using the 75 per cent. which he has to do for the ordinary duties of life, he has only a narrow margin of 25 per cent. for extra calls and emergencies. All circumstances that tend to depress the vitality and to lower the nutrition must be avoided, and he must be taught to adjust his life to his heart's capacity, or, in other words, to live within his cardiac income. For a young, energetic, muscular individual this is a hard lesson, and it becomes a serious problem how to adjust in proper measure exercise and diet, in the varied conditions in life.

TREATMENT OF CARDIAC INSUFFICIENCY.

During the establishment of compensation certain troublesome features are apt to arise which require treatment. It is not always easy to say just how far these depend upon the hypertrophy and dilatation themselves and how far upon associated neurotic states. Not infrequently we are consulted by young men or young women between the ages of fifteen and twenty who complain of uneasy sensations about the heart with throbbing and palpitation, sighing respiration, and sometimes shortness of breath on exertion. On examination, signs of slight enlargement of the heart with overaction are present. This is really the well

known irritable heart of the young, or some speak of it as the developmental hypertrophy. Sometimes it would appear as if there was a disproportion between the growth of the heart and of the body. Overexertion, particularly in schoolboys and in young collegians, cigarette smoking, masturbation, and overuse of the bicycle are sometimes causes. The outlook in these cases is usually good. They should avoid overuse of the muscles, and tobacco should be interdicted. They should be moderate in diet and the state of the heart should be carefully watched. It is not always well to make too much of the condition. Very often the unpleasant sensations of abnormal action are quickly relieved by lessening the diet, cutting off the more starchy articles of food and anything which causes flatulency. In other instances a few doses of spirit of camphor or aromatic spirit of ammonia may be needed, but, as a rule, all that it necessary is a careful regulation of the life.

Overcompensation is a condition not infrequently met with in the early stages of valvular lesions before the heart has, so to speak, "found itself." Unpleasant throbbing, with irregular action, feelings of fulness in the head, inability to rest comfortably in the recumbent posture, are among the improtant symptoms, or the patient may have severe nocturnal attacks of palpitation. Very often this is not so much due to anything in the heart itself as the associated nervous state or anemia. Rest in bed for a week with careful regulation of the diet may be enough; if the heart's action is very violent, an ice-bag may be placed over the precordia for half an hour at a time. There are cases in which this unpleasant feature persists and is a source of more or less constant annoyance.

The actual valve lesion, of whatever nature, is very little under the control of treatment. Prolonged rest and potassium iodide influence the acute proliferative valvulitis, but we cannot replace scar tissue nor can we dissolve calcified atheromatous plaques. The whole treatment revolves about the cardiac muscle, the establishment and maintenance of compensation, the relief of the symptoms of insufficiency or decompensation, and the treatment of certain special symptoms.

1. **The Establishment and Maintenance of Compensation.**—Given a free coronary circulation, even in a state of wretched nutrition, the heart will gradually accommodate itself to the most severe valvular lesion. The hypertrophy and dilatation are not only salutary, but without them the circulation could not be maintained. As a rule, the call for additional strength comes slowly, and, as already mentioned, it is the old story of the woman who carried a calf in her arms every day, so that when it was an ox she still could carry it. So in the slow onward progress of a valvular lesion, month by month, year by year, the daily strength becomes equal to the daily needs. One point at the onset comes up in nearly every case: should the patient know of the existence of the disease? Most assuredly: It is impossible to carry out rational measures without his intelligent coöperation. The exceptions to this rule are very few. Occasionally a neurotic subject is upset and is frightened to perform the ordinary duties of life. One or two such instances have come under my observation; individuals who have had a perfect obsession about

the heart lesion, a sort of pantophobia which has made of them wretched valetudinarians. In many cardiac conditions, however, it is neither necessary nor advantageous to tell the patient of the state of his heart. In the hypertrophy of arteriosclerosis or of chronic Bright's disease, or of a chronic pulmonary affection, no special benefit is derived from laying special stress on this feature of his case.

In the case of a young man, the first thing to be considered is his calling. Very often it has been at a special examination for some service that the valve lesion has been detected. Under these circumstances he is excluded from a certain number of occupations, and he should, if possible, choose one in which the demands upon the muscles are not great. In the working-class this is, of course, a great difficulty; but, if possible, trades and occupations requiring much exposure and hard work with the muscles should be avoided. In the higher classes, the professions with least strain, the clerical, the legal, and the occupations in which the work is sedentary, may be taken up. For persons with a little capital, who have not themselves to do the heavy work, gardening and small farming are very suitable.

To maintain compensation the *diet* should be simple, avoiding, in particular excess of food. Often in the early stages the patients are anemic and feeble, so that they require an abundance of good food, with plenty of milk and eggs, meat, and fresh vegetables. If there is a tendency to put on fat, the diet should be restricted in carbohydrates and the patient should not be allowed to take too much food. Beer and spirits are quite unnecessary. In middle-aged men with aortic incompetency, if they have been accustomed to much spirits, a glass of whisky may be allowed at dinner. *Tobacco* may be used in moderation, but in young men it is best interdicted, so difficult is it to keep the use in moderation, and even two or three cigars or half a dozen cigarettes may cause irregularity. Tea and coffee may be taken in moderation, a single cup of coffee at breakfast and a cup of tea or coffee in the afternoon and another after dinner. No strict rule can be laid down about this, as even these small quantities may cause irregularity. The question of *exercise* is always the most important in connection with valvular disease, and it is not at all easy to reach a happy medium. It should be understood that in a great majority of well-compensated lesions, moderate exercise is of advantage. Regular systematic exercise, as in walking, easy cycling, horseback exercise, and golf, may be taken. For young men, the more violent sports should be interdicted. Golf is a particularly suitable game for men of all ages with well-compensated lesions. They should be warned not to overdo it and not to play to the limit of tire, and the test of damage is the occurrence of dyspnœa or exhaustion. When outdoor exercise cannot be taken, systematic gymnastic movements may be employed. One is constantly asked, in the case of young girls, about *dancing*. With a simple mitral lesion perfectly well compensated and the apex beat not very far out, it may be allowed in moderation. Each case must be decided by itself. There are many instances in which it has not been at all hurtful. Hill-climbing and walking in the Alps may be very beneficial if not pushed to an extreme. After all, the test of any

exercise is the result. If the patient is helped by it, if he is not made short of breath when at rest, or if it does not cause attacks of palpitation or nocturnal dyspnœa, it may be continued. As a rule, patients with valvular lesions should not go to very high altitudes. This is a good rule, to which, however, there are many exceptions. In a well-compensated mitral lesion there may be no difficulty. On the other hand, the patient may feel a good deal of distress at any altitude above 6000 feet.

Special care should be taken of the *bowels*, and if there is any tendency to corpulency an occasional saline purge may be used. The skin should be kept active by a daily bath. A cold tub in the morning may be taken if there is a good reaction afterward; if not, a lukewarm bath at night. Very hot baths should be avoided. Young people should be allowed plenty of sleep, and in the early stages of well-established compensation an hour's rest in the middle of the day is helpful. It is impossible to lay down hard-and-fast rules to meet every case, but the physician should try to reach the happy medium between overanxiety and unnecessary precaution, and allowing the patient a liberty which may lead to early decompensation. "Moderation in all things" should be the motto of the patient.

Two or three special points may be referred to. The question of *marriage* is always a distressing one, particularly if before the onset of the lesion the patient's affections have been engaged. Everything depends upon the lesion and the stability of the compensation. In young women with simple mitral incompetency there seems to be a minimum of risk. In many such cases they become the mothers of large families without the slightest damage to the heart lesion. It is to be remembered that often a lesion reaches a stationary point and the heart is really a first-class piece of mechanism, with only 50 per cent. less reserve than in a normal one. Always in this connection the writer calls to mind a patient who has been under his observation for many years, in whom a mitral insufficiency followed rheumatic fever at sixteen. With a loud apex systolic murmur, and signs of moderate enlargement of the left ventricle, this woman has had nine children and has lived to be more than sixty years of age. The extreme mitral stenosis is not so favorable, and yet in how many instances has one seen repeated pregnancies safely carried through with quite advanced stenosis. Combined mitral and aortic disease, with great enlargement of the heart and tumultuous heaving of the chest wall and slight protrusion should interdict marriage. The middle-aged Lothario who is shocked to find (perhaps as the result of a life insurance examination) before the contemplated marriage that he has an aortic insufficiency, should be warned of the dangers. But these are cases in which, if the physician is wise, he will simply express an opinion on general grounds, as his specific advice is almost certain not to be taken.

In young persons special pains should be taken to prevent *intercurrent diseases*. In children the condition of the throat should be watched with the greatest care, and if there is the slightest enlargement of the tonsils it would be better to have them thoroughly removed. The state of the mouth should be carefully watched, bad teeth removed, and a

visit to the dentist should be paid once in three months. When possible, for a year or two after the establishment of compensation the patient should be carefully watched, and during the winter months a change of climate is most helpful—to Florida, Southern California, the South of France, Italy, Egypt, or Algiers.

2. **Treatment of Loss of Cardiac Compensation.**—At any stage in a valvular lesion, or in hypertrophy and dilatation of the heart from any cause, *acute cardiac insufficiency* may arise, associated with dyspnœa, more or less cyanosis, irregular action of the heart, the gallop rhythm or embryocardia and a small, rapid pulse. In typical form this is seen in the cases of arteriosclerosis, in hypertrophy and dilatation from overexertion, but it may occur in any form of valve lesion. It is the one condition in heart disease in which a venesection is advantageous. In many hands it is not satisfactory, because sufficient blood is not taken. Good results are rarely seen unless as much as twenty ounces is taken. To "breathe a vein" skilfully is now almost a lost art, and to get enough blood it is sometimes necessary to bleed from both arms. Hypodermics of ether in dram doses, strychnine hypodermically in $\frac{1}{30}$ or $\frac{1}{20}$ grain (0.002 to 0.003 gm.), or digitalin, $\frac{1}{20}$ to $\frac{1}{12}$ grain (0.003 to 0.005 gm.), may also be given. Camphor, either by the mouth (the tincture in dram doses) or hypodermically, in doses of 2 grains (0.13 gm.) dissolved in olive oil, is useful. Local applications to the heart may be tried, a hot-water bag as hot as can be borne, or a mustard leaf. If the case seems desperate, cardiocentesis may be practised. The needle is thrust boldly into the heart substance in the fourth or fifth interspace. Reading the successful case reported by Sloan some years ago, one cannot but feel that this measure, desperate though it seems, may occasionally be useful. The senior author has only practised it twice himself, in neither instance with any special benefit.

In a majority of intances the failure in compensation is gradual, and it takes a week or two before the signs are well established. The first and all-essential requisite is:

Rest of the body may, indeed, be the only thing necessary. Time and again, to demonstrate its importance to students, the senior author has treated patients with this measure alone, combined, perhaps, with a brisk saline purge, and within a few days the œdema of the feet disappears, the bases of the lungs become clear, and the heart's action quiet and strengthened. In many instances the chief value of a consultation has been in the insisting upon absolute rest. It is not always possible to induce a patient to go to bed, nor is it always possible for him to remain in bed. In the milder grades of cardiac breakdown the semirecumbent posture may be maintained, but it too often happens that the condition is one of orthopnœa, and there is no possible position of comfort in bed. The patient then has usually to sit up out of bed, and he is fortunate if there is available an old-fashioned "grandfather's chair" with the comfortable side pieces for the head. One of the greatest difficulties in the nursing of these cases is to get a position in which the patient may sleep comfortably. Too often just as he drops off, the head falls and he wakens with a start. An ingenious nurse may some-

times be able to advise methods for the support of the head, but it is by no means easy. Sometimes these patients get into all sorts of remarkable attitudes. One poor fellow with a cardiac breakdown following emphysema had comfort only in the knee-elbow position. Patients may be able to sleep kneeling at the side of the bed. One man for weeks could get relief only by leaning forward on to the back of a chair against which he rested his forehead, on which, in spite of every precaution, he had a bedsore. The greatest care should be taken of the back, but nowadays, with modern nursing, one rarely sees the terrible bedsores which were common thirty or forty years ago. Sooner or later, there comes a stage when there is more or less permanent cardiac insufficiency which neither rest nor medicinal measure is able to overcome. The patient is tired of bed, and under these circumstances it is often beneficial to let him be up and about for part of the day, even if the exercise does bring on shortness of breath and increase the irregularity of the heart. In these chronic cases, when possible, the bed should be wheeled out-of-doors, or they may sit up on the couch on the veranda for part of each day, or be taken out in a wheeled chair. The question of systematic exercise will be considered in connection with the special methods of treatment.

Diet is one of the most important and at the same time difficult elements in the treatment. We have all been notorious sinners in overfeeding our heart patients, particularly in the stage of broken compensation. The stomach is not only a near but a bad neighbor to the heart. With venous stasis of the gastric mucosa it is impossible to have a good gastric juice, and it is a good rule for the first few days, when the patient comes under treatment, to give a minimum quantity of food until with saline purges, the overloaded viscera are relieved. A patient will get along perfectly well with the whites of six to ten eggs, flavored with lemon; this is very palatable, and in three or four of the feedings a little whisky or brandy may be given. Freshly prepared beef juice, milk diluted with lime-water or soda-water, and whey are also suitable. Not too much should be given, and when there is nausea or vomiting it will do no harm to let the patient go for twelve hours without any food in the stomach, and at intervals very hot water may be given, and if it be thought necessary, rectal enemas may be used. All prepared starchy foods are, as a rule, contra-indicated. Patients differ very much in their tastes and gastric capacities, and to a certain extent these may be humored. As soon as possible the patient should be taken off the "slops" and given solid food in small amounts; care should always be taken not to fill the stomach too much with liquids and solids at the same time The sensible doctor will not forget that even a perfectly healthy stomach could not stand the heroic medication which we sometimes encounter, three mixtures—necessitating a dose at least every two hours, often a nocturnal pill, the nocturnal purge, the morning saline and sleeping draught at night. Too often this Arabian polypharmacy defeats the very object we have in view.

Reduction of Intake of Liquids.—It is by no means easy to decide just in what class of cases liquids should be restricted. Theoretically, the ingestion of large quantities of fluid increases greatly the work of

the heart, but there are many conditions in which it seems necessary in order to promote diuresis and sweating to give large quantities of fluids; milk, barley-water, and fluids generally. The following may be taken as indications, but they must be modified to suit the conditions. When compensation is good the patient should be careful not to take too much liquid, but the quantity of urine should not be allowed to fall below a normal limit. Such patients should not be allowed to take "cures" indiscriminately, as the drinking of very large amounts of liquid may lead to pronounced embarrassment of the heart. In very stout patients with valvular or myocardial lesions, the meals should be taken as dry as possible, and fixed quantities of liquid given during the day, enough to keep up the output of urine. The cases which demand reduction of the liquids are those with cardiac dilatation and venous stasis and œdema. Combined with purgatives, the reduction in the total of the liquids to one and a half pints given at stated intervals, either milk and soda-water or milk and barley-water or albumin-water, may have a very beneficial effect on the dropsy and promote the flow of urine; under these circumstances, too, the digitalis acts more favorably, as well as other remedies, such as diuretin.

Special Methods.—Certain plans of treatment have been introduced —combinations of diet, exercises, and baths.

Oertel's Method.—The late Professor Oertel, of Munich, who had a vast experience with the heart lesions of stout, beer-drinking Germans, devised a method of treatment which is often most satisfactory in the weakened heart of obese persons. He sought to reduce the quantity of blood, to increase its concentration, and to diminish the amount of fat. The treatment consists in, first, the reduction in the amount of liquid. A total of about 36 ounces is allowed in the twenty-four hours, which includes the amount taken with the solid food. Baths and sweating help still further to reduce the quantity of water in the body. Secondly, the diet, which is chiefly protein:

Morning.—Cup of coffee or tea, with a little milk, about 6 ounces altogether. Bread, 3 ounces.

Noon.—Three to 4 ounces of soup; 7 to 8 ounces of roast beef, veal, game, or poultry; salad or a light vegetable; a little fish; 1 ounce of bread or farinaceous pudding; 3 to 6 ounces of fruit for dessert. No liquids at this meal, as a rule, but in hot weather 6 ounces of light wine may be taken.

Afternoon.—Six ounces of coffee or tea, with as much water. As an indulgence an ounce of bread.

Evening.—One or 2 soft-boiled eggs; 1 ounce of bread; perhaps a small slice of cheese, salad, and fruit; 6 to 8 ounces of wine with 4 or 5 ounces of water. The third and most important are exercises, the so-called "*Terraincur.*" Graduated walking exercises are taken, not on the level, but uphill at various grades. A definite amount is done each day and the distance is gradually increased. Undoubtedly, at proper resorts suitable cases are greatly benefited by this plan of treatment, but it is to be borne in mind that Oertel recommended it particularly for the stout individuals with weakened heart action.

Nauheim Method.—Here the great influence is believed to be effected through the stimulating influence upon the heart of hot CO_2 saline baths combined with special muscular exercises. The precise mode of action is still under discussion, some attributing the good results to the stimulating influence of the CO_2 on the nerves of the skin; others regard the temperature of the bath as the most important element. Whatever the precise *modus operandi*, the heart is stimulated to more vigorous contraction and the area of heart dulness is diminished under observation. It has been suggested that this may be only the effect of Abraham's cardiac reflex. By reducing the temperature of the bath and increasing the concentration of the salts, the heart's action is still further stimulated, and it becomes progressively strengthened. Resistance exercises are given by a trained attendant, and definite groups of muscles are systematically brought into action.

Nauheim has become a vogue, and all sorts and conditions of patients from all parts of the world flock there, so that it is by no means easy to form an unbiased judgment on the value of the method. The senior author has been watching carefully the results in many patients who have been under treatment there. They may be divided into three groups: Scores of persons who have nothing whatever the matter with their hearts are greatly benefited by the change and the holiday. In a second large group much damage is done. For years the senior author has been in the habit of seeing victims of the Nauheim cure, many of them physicians, who have come for advice regarding the long train of troublesome symptoms of the neurotic heart. Frightened by a little irregularity, they have submitted themselves to a Nauheim "cure," and have been greatly alarmed to find that instead of improvement, they have grown worse. In many neurotic women the last state has been much worse than the first. As a rule, these patients are little if at all benefited. Cases of aneurism, valvular disease in the late stages of broken compensation, arteriosclerosis with very high pressure, do not seem to do well under this method.

A third group, in which good results are seen, comprises the chronic myocardial cases, the fat patients with weak hearts, and the cases of valvular disease with slight disturbances of compensation, but not with dropsy. The baths may be carried out at home, but the same beneficial results are rarely obtained, even in suitable cases. As so often happens in these special forms of treatment, an opportunity is given for unscrupulous practitioners to impose upon patients, and the Nauheim method has not always been carried out with common-sense. A plentiful lack of judgment has characterized the treatment of many individual cases that have come under observation. One thing should be demanded of those who carry out the treatment at Nauheim or elsewhere: they should stop alarming people who have little or nothing the matter with their hearts.

Medicines which Strengthen the Heart's Action and Help to Restore Compensation.—Among these digitalis not only takes the first rank, but is in a class apart. Evidence has been accumulating to show with much greater accuracy the effect of digitalis on the various functions of

the heart. *Excitability* is not a function which is affected to the same degree as the others, yet the frequent presence of *pulsus bigeminus* is evidence of a hyperexcitability of the ventricle and the production of an extrasystole in the more rhythmic parts of the ventricle. The second beat in pulsus bigeminus is never preceded by an auricular beat. Digitalis occasionally causes extrasystoles to disappear. When the drug causes their appearance, either irregularly or in the form of a coupled rhythm of the pulse, it is evidence according to Norris, of calling upon the cardiac reserves, and though improvement may be manifest the drug should be stopped.

The effect of digitalis on *contractility* is one of the greatest dangers of its action. The action of digitalis in producing a pulse just half the rate of the ventricle is well known. This is due to a depression of the function of contractility, and gives rise during the earlier stages to the condition known as *pulsus alternans*. If its action is allowed to continue, it produces half the rate of beat in the arteries, the second beat being unable from its feebleness to produce a wave in the arteries. Later the second beat may be entirely suppressed even at the heart. Wenckebach's explanation is that the normal depression of contractility which follows each beat is much greater under the action of digitalis, and that when the second stimulus from the auricle reaches the ventricle the latter is only able to respond in a feeble manner. In certain cases digitalis has caused *pulsus alternans* to disappear.

Conductivity is a function which has been shown by Mackenzie to be markedly depressed by digitalis. When such an effect is present, it takes the form of lengthening the interval, normally about one-fifth of a second, between the beginnings of the auricular and ventricular impulses. It produces exactly the same effect as gradual mechanical compression of the auriculoventricular bundle in the dog (Erlanger), and results in a dropping out of certain ventricular contractions and is due to an effect chiefly upon the vagal apparatus but also partly upon the muscle. But in some cases digitalis does not produce an effect on conductivity, unless given in enormous doses, which points to involvement of other factors. Of the effect of digitalis on *tonicity*, there is the invariable clinical observation that it is of the greatest use when dilatation is present, and the benefit which comes from it is due to a stimulation of this special function of the heart muscle. It may be taken as a guiding rule that digitalis will not do any good unless dilatation is present. The early slowing of the heart when digitalis is administered is due to its effect on *rhythmicity*. The longer diastole allows of a much greater restitution of the other functions, especially that of contractility, and the whole cardiac mechanism is benefited.

Digitalis is indicated when the heart's action is weakened to the degree of insufficiency. Neither feebleness of action nor irregularity are in themselves indications. Not until the effects of such weakness become manifest in shortness of breath, cyanosis, or œdema is the drug indicated. As a rule, the type of valvular lesion makes no difference whatever, as the cardiac insufficiency, for which the digitalis is almost a specific, is an affair of the muscle, not of the valves. In the common,

triple combination characteristic of insufficiency—dyspnœa, venous stasis, and dropsy—experience has fully borne out the ninth inference of Withering, "that digitalis has a power over the motion of the heart to a degree yet unobserved in any other medicine." According to more recent knowledge, its effect is seen best in auricular fibrillation of rheumatic origin. In the arteriosclerotic form its benefit is not so marked.

In cases of acute cardiac insufficiency the good effects are not so striking, the patients admitted in a state of cyanosis and orthopnœa and embryocardia are much more promptly relieved by copious venesection. The results of the administration of the drug are often phenomenal. The patient, who has been in a desperate state, may within a few days be rendered comfortable.[1] Relief of the thoracic oppression and of the dyspnœa, lessening of the cyanosis, and increase in the flow of urine are the indications of beneficial action.

The *contra-indications* for the use of digitalis are much more numerous than the indications. Few valuable drugs are so much wasted. Neither rapidity of action nor arhythmia are in themselves indications, unless accompanied by signs of weakness of the muscles. There are many cardiac irregularities over which digitalis has no control, and persistency of irregularity is neither a contra-indication nor an indication for its use. In many cases the signs of heart failure in mitral disease disappear under its use, while the irregularity persists. It may be said broadly to be contra-indicated in all forms of heart disease without symptoms of muscle weakness; it is contra-indicated, too, in the great majority of cases in which the patients come complaining of their heart, of irregular and violent action. Such cases are much more satisfactorily treated by attention to their digestion and the nervous condition. In states of high arterial tension, one is sometimes placed in a quandary, as the paradoxical features may be presented of a dilated heart with gallop rhythm and blood pressure considerably above the normal. Under these circumstances the latter may be discounted. But in middle-aged men with permanent high tension, sclerotic vessels, and a hypertrophied left ventricle, digitalis may be directly hurtful. In angina pectoris, as a rule, the underlying conditions are not those which are modified by digitalis. In a few cases in which the heart's action is feeble, gallop rhythm is present, and particularly when the angina is directly associated with a very old valve lesion, more particularly in mitral cases, digitalis may be used without risk. In aneurism the drug is not of any service, except in rare cases when the dyspnœa and œdema are directly due to heart weakness. There is widespread belief in the profession that digitalis is contra-indicated in insufficiency of the aortic valves. In the periods of decompensation the drug more frequently fails than in corresponding mitral cases, and we more frequently see death in heart cases in aortic insufficiency during the administration of digitalis; but this is particularly in the arteriosclerotic group when the nutrition of the heart muscle is

[1] For the young physician there is no other reputation-producing medicine of the same rank with digitalis, and it is one of the dozen drugs the uses of which repay a lifelong study. How he uses it may be taken as a sort of indication of the therapeutic intelligence of the practitioner.

failing, and when, as so often happens, the coronary arteries are seriously involved. In a majority of instances just as good results are seen in this lesion as in mitral cases, but a little more care has to be exercised in its use.

With the common gastric disturbances of broken compensation, digitalis, as a rule, is not well borne, as it often aggravates nausea and vomiting. Under these circumstances it is much better given hypodermically. Toxic symptoms, which are not very often met with, follow the employment of very large doses or, occasionally, the prolonged use. Nausea, vomiting, sometimes diarrhœa, with pallor of the face, feeble, rapid pulse, and dimunition of the amount of urine are the special features. There are three useful indications when the patient has had enough digitalis. The pulse becomes slow, but it must be remembered that one of the characteristic actions of the drug is the production of the bigeminal pulse. The second beat may become feebler, and finally is not perceptible to the finger. It may at the same time be evident as a small beat in the tracing, and the corresponding sound may be heard at the apex. The pulse may be counted at 40 when the heart beats are 80, or at 60 when they are 120. Mackenzie, Hewlett, and others have studied this peculiar action of digitalis, which may produce a definite type of heart-block. Hewlett has reported cases which seem to show that the combination of atropine prevents this effect. The condition is common in mitral cases, and may keep up for weeks without any special risk, but it may be followed by a rapid feeble action of the heart. The second important indication is a lessening of the flow of urine. Directions should always be given to measure and record the daily quantity, as a reduction gives one of the earliest indications when the useful action of the drug on the heart and vessels has ceased; and thirdly, a progressive lowering of the blood pressure is, as a rule, an indication to stop the drug.

Mode of Administration.—The judicious practitioner will study the use of three or four preparations which have stood the test of many years and will look askance at many of the new-fangled preparations of the drug.

The Tincture.—In a patient with mitral or aortic lesion, who has just begun to have shortness of breath with swelling of the feet and diminution of the amount of urine, a good plan is to give the tincture in 15 minim doses every four hours for two days. Then it may be stopped for twenty-four hours and resumed for another two or three days, and so continued at intervals. Usually within ten days or two weeks the serious symptoms have disappeared and the drug may be stopped, or continued in 5 minim doses three times a day. As a rule, the tincture answers admirably, unless the stomach is very irritable.

The *infusion* in half-ounce doses, four to six times a day, is equally efficacious, and is believed by some to be more diuretic in its action. When the stomach is irritable it is not so well borne.

Powdered digitalis is of great service, in combination with squill and mercury, a grain of each in the form of the Addison or Guy's pill. It is particularly indicated in the cardiac failure of old arteriosclerotic

patients, those with chronic nephritis, and more particularly when there is swelling of the liver, ascites, and jaundice.

The so-called active principles of the digitalis, digitalin, and digitoxin have been much used. The only advantage of digitalin is that it may be given hypodermically when the stomach is irritable. To get any good effects from the ordinary digitalin (Merck) it must be given in large doses, $\frac{1}{30}$ to $\frac{1}{20}$ or even $\frac{1}{12}$ grain (0.002 to 0.003 to 0.005 gm.) every four hours, watching its effects carefully.

For how long may digitalis be used without danger? There is not much risk of cumulative action with sudden untoward manifestations. As a rule, the symptoms above referred to suggest at once that the patient has had enough. Twice the senior author has known the digitalis habit to be contracted, in which over a long period of years patients took the tincture, in one case 5 and in the other 10 minims two and even three times a day. One was a physician with aortic insufficiency, who had taken digitalis daily for more than twenty years as he had a fixed idea that without it his heart became feeble.

Substitutes for Digitalis.—There are none, but it occasionally fails and there are other remedies which have an action on the heart of the same character, but less constant and enduring. Among those strophanthus takes the first place. It may be used in the form of the tincture, of which 10 minims (0.6 cc.) may be given every three or four hours. Its constricting effect upon the smaller arteries is said to be less than digitalis. It is very often useful to keep up the action of the heart after a course of digitalis, and in children with old mitral lesions it is sometimes better borne. As a rule, it is rarely found to be efficacious when digitalis fails. Strophanthin has been much used of late for obtaining the same end as digitalis in a shorter time, either preliminary to a course of this drug or in case the reaction of the heart to it has failed. It is injected intravenously in doses of from 0.1 to 0.5 milligram and may be given intramuscularly in the same doses. The cases should be carefully chosen and it should not be given in chronic nephritis. Sparteine, in 1 grain doses of the sulphate, adonis vernalis, and convallaria may be sometimes useful. Camphor is much used by the Germans; caffeine and theobromine are also recommended, but in failure of the heart muscle they are not of much value in comparison with the preparations of digitalis. Strychnine by mouth or hypodermically in acute conditions is often of service, and may be given with the other remedies. Depending on the condition, it may be given in doses of $\frac{1}{60}$ to $\frac{1}{20}$ grain (0.001 to 0.003 gm).

3. **Treatment of Special Symptoms.**—Cardiac *dropsy* is usually relieved by the digitalis. When resistant, it forms one of the most difficult symptoms to overcome. The use of the saline laxatives, particularly the salts given in concentrated form early in the morning, the compound jalap powder, or calomel purges, are very helpful. To promote sweating, hot baths, either the very hot tub, the steam bath, or the hot-air bath, may be tried cautiously. On the whole, it may be said that this is not so satisfactory in cardiac as in renal dropsy, and it is sometimes very difficult to get a profuse action of the skin. The hydrothorax and ascites

may require tapping. If the anasarca of the legs becomes very great, the skin may be punctured either with the small Southey's trocar, or small incisions may be made in several places on the legs. Dressed with gauze and thick layers of sterilized cotton, an enormous amount of fluid may be drained away. It is, as a rule, perfectly safe when the usual precautions to avoid infection are taken. In milder grades of the anasarca it is very helpful to bandage the legs firmly.

Sleeplessness and Restlessness.—With failure of compensation the patient has almost always bad nights, and the question of the use of hypnotics comes up at an early date. It is well at first to try the milder forms. Paraldehyde is often very satisfactory, given in dram doses; the patients become accustomed to the unpleasant odor. Veronal or trional alone or combined with potassium bromide may be tried. Chloral hydrate is often useful. When the milder hypnotics fail, as they often do, opium should be used. While it is contra-indicated with a low output of urine and the presence of a great deal of bronchial catarrh, it is perhaps next to digitalis the most favorable drug in the treatment of the heart itself. In the cardiac failure of arteriosclerosis, with the terrible nights of orthopnœa and restlessness, hypodermics of morphia give the greatest relief. We are, altogether too cautious in the use of this drug, which is of incalculable service in the severer manifestations of the disease. Given in small doses of $\frac{1}{8}$ grain (0.008 gm.) hypodermically it may be repeated in a few hours if rest is not obtained. In children paregoric is very helpful, and it may also be used in the attacks of nocturnal palpation in the irritable heart.

Anemia.—This should always be kept in mind, and if present, iron and arsenic should be given as soon as the acute cardiac features are over. Some patients are greatly helped by occasional courses of these drugs.

CHAPTER IX.

FUNCTIONAL DISEASES OF THE HEART.

By CHARLES F. HOOVER, M.D.

The prognostic distinction between anatomical and functional disease of the heart is not so sharply drawn as in former years. Anatomical diseases of the heart were formerly the only cardiac affections which were linked with grave prognostic significance. Functional disturbances of the cardiovascular system were in former years not associated in the minds of medical men with heart death. Our present conception of functional disease of the heart is not at all inconsistent with the ultimate death of the heart. Even in heart death following organic disease we are now becoming more accustomed to the conception of functional death of the heart, separate from the idea of an exhausted muscle struggling against great odds.

Attention has been directed to the failure of diastole, in contrast to the failure of systole, at death of the heart, so that this idea of heart death from disorder in the nervous impulses to the heart enters more and more into our conception of the natural history of heart diseases. Anatomical diseases of the heart may precede a functional disturbance, but, on the other hand, a functional disease of the heart may terminate in an anatomical disease. We know the persons most frequently affected by diseases of the heart muscle and vascular system are those who in early life have suffered from neurasthenia or hysteria, or by their mode of life have subjected the neurovascular system to oft-repeated insults, which, although apparently mild in their single events, have produced, collectively, final histological changes in the myocardium and aortic system. It is a common practice of physicians to console patients with the remark, "The heart is of normal size and the sounds are clear." Many of the laity have learned that such an assurance offers little consolation. We see some instances of myocardial incompetence following prolonged intense mental and emotional distress. One instance was in a patient with a rapid, irregular, and slightly dilated heart, but there was nothing further in the physical status to account for the myocardial disturbance. It was learned that the social condition of the patient was extremely bad; she had been suddenly reduced to want and had lost several members of the family by death. A few months later the woman appeared with a perfectly rhythmic heart and normal percussion lines. The social distress of the patient was relieved in the meantime, and with this relief the cardiac distress disappeared.

Many damage suits involve the question of whether the patient's heart affection is due to a lesion or merely functional disturbances which have resulted from mental shock. These evidences of cardiac disturb-

ance are frequently very difficult to classify. All of these instances of cardiovascular disturbances which come under the head of traumatic neuroses and those which follow upon prolonged and severe mental distress must be regarded as the direct result of an unfavorable influence on the cardiac innervation through the cerebral cortex; but there are many symptoms in the circulation which result from unfavorable influences on the cardiac nerve centres from impulses in remote nerve distribution—for example, the cardiac neuroses which accompany disorders of the abdominal and pelvic viscera. Our knowledge of nerve paths involved in cardiac innervation compels us to regard both classes of disease as reflex in character but both may eventuate in anatomical lesions and in heart death. If we consider the very severe treatment applied to nerve paths in animal experiment before we can elicit tachycardia, bradycardia, and cardiac arhythmia, the very symptoms which we commonly see as a result of severe mental distress, prolonged emotional excitement, or disease of the gastro-intestinal tract or pelvic viscera, we may have some conception of the severity of nerve impulses in these affections which we are apt to treat too lightly in nervous patients.

Tessier reported a case which has an interesting significance relative to trophic and functional disturbances in the heart attending diseases of the nervous system and traumatic neuroses. This patient had traumatic cervical spondylo-arthritis attended with dilatation of the right heart, arhythmia, and a loud systolic murmur; all of which disappeared after recovery from the symptoms in the cervical vertebræ. The cardiac signs in this instance did not appear until nearly two months after the accident and developed simultaneously with the signs in the cervical vertebræ. Symptoms having an anatomical and functional basis are sometimes intimately linked in the reverse sequence. We may have primarily anatomical disease, but frequently with it we have manifestations of severe functional disturbances which must have their basis in nerve structures more remote than the apparent anatomical lesion. We commonly see in the early stages of tuberculosis a rapid heart rate which we interpret as being due to toxins of the tubercle bacillus or enlarged tuberculous glands in the mediastinum.

Martius, in his monograph on tachycardia, criticized the attempts to account for the rapid heart rate as a disturbance of the balance between the vagus and cardiac accelerator nerves. The basis of this criticism is the failure to produce paroxysmal tachycardia by severing a heart from its inhibitory fibres. Martius further states that if tachycardia be due to vagus disease, such as must result from direct pressure of mediastinal glands, then the tachycardia could not be paroxysmal in type, but must be constant. Martius' position is not confirmed by the clinical experiences of others. There are a number of cases reported and two instances have come under personal observation in which paroxysmal tachycardia was implanted on a constant tachycardia resulting from tuberculosis of the mediastinal glands. We find also that functional disturbances in regions of the vagus supply (other than the heart) may be paroxysmal in character, when pressure from the mediastinal glands is the cause. Neusser reports a case in which paroxysms of meteorism accompanied

the paroxysmal cardiac symptoms. Another instance which came under the writer's observation was in a girl, aged eight years, who for two years had marked signs of tuberculosis of the anterior cervical and mediastinal lymph glands. The autopsy revealed a mediastinum packed full of tuberculous glands in various stages of caseous softening. For two years the child had been subject to attacks of spasmodic asthma which were very severe and came as a rule with abrupt suddenness and lasted from thirty minutes to an hour, and then ceased as abruptly as they appeared. After these attacks the child ran about and played as she had done up to the time of the seizure. During the last two years of life, this child had an attack about once a month. In the intervals she had slight cough. She was pale and poorly nourished, but otherwise nothing attracted the parents' attention. The writer saw the child in her last asthmatic attack. The child was profoundly cyanotic and presented all the objective signs of asthma with acute pulmonary emphysema. The cardiac rate during the attack was 140. Quite suddenly all respiratory distress ceased. The asthmatic breathing was replaced with easy inspiration and expiration, and quite as suddenly the lower border of the lung ascended two inches. Within a few seconds there was sudden transition from severe bronchial asthma with emphysema to perfect respiratory comfort and normal lung volume. All traces of cyanosis disappeared in the fraction of a minute. The heart rate, however, remained the same and the child seemed very much prostrated. Sudden death occurred half an hour after the respiratory distress ceased.

Paroxysmal disturbances of cardiac rate and rhythm are sometimes superadded symptoms in the course of organic diseases. Coincident with the gastric crises of locomotor ataxia, paroxysms of tachycardia may occur. A heart rate of over 200 per minute may suddenly develop, which persists from a half to twenty-four hours and ceases as abruptly as it commenced. Disturbance in the cardiac rhythm is one of the commonest clinical aspects of valvular disease, although in addition to the usual disturbances of rate and rhythm we may sometimes have paroxysmal tachycardia. This has been observed in patients with mitral stenosis and aortic insufficiency. The method of onset of attacks in such cases is very similar to that in essential paroxysmal tachycardia and tachycardia from reflex sources. In disease of the myocardium we may have either an increase in the rate or bradycardia, but in addition to the moderate tachycardia so common in myocardial diseases, there are also paroxysmal attacks of tachycardia which begin with a few pulses of the vagus character or extrasystole, and are succeeded directly by a heart rate as high as 240. A woman, aged fifty-six years, presented a clinical picture of myocarditis which followed a lobar pneumonia six years before. Although she was quite anxious and fretted much over the limitations which her myocarditis placed upon her, the phase of the disease hardest for her to endure was paroxysmal tachycardia, which recurred during the six years at intervals of one to two months. The onset was very abrupt in all the attacks. The abatement, however, was very gradual and lasted over a period of about one-half hour. The duration of the attacks was usually as long as ten hours. With the

exception of the gradual abatement the attacks were identical with paroxysmal tachycardia from other sources. In all of the instances cited—namely, disturbances of rate and rhythm from the cerebral cortex, from the basal ganglia, from the cervical cord, from the vagus trunk, and from the myocardium itself, there is a certain constancy in the clinical picture which makes it appear as though they have in common an ultimate nervous mechanism, probably through the bulbar centres.

The question of autonomy of the heart being myogenic or neurogenic is inseparable from the discussion of changes in heart rate and rhythm from any cause. The champions of the myogenic theory have shown how independent the heart may be of all connection with the central nervous system, as is shown by an animal surviving eleven months after all connections of the heart with the brain, spinal cord, and sympathetic nervous system were severed. Wave transmission within the myocardium independent of any nerve contact is apparently shown by the series of sections through the heart's muscle which sever all continuity of nerve paths from the base to the apex of the heart and yet it maintains muscular continuity through narrow muscular connections. The embryologists have been able to show that the rhythmic beat of the heart occurs before any nerve structures are found in the heart itself, and Hering and others have shown how the resuscitation of the heart, after removal from the body, seems dependent upon metabolic processes within the myocardium. Anyone who follows the work of the physiological laboratory will be impressed with the fact that experiments so far have not succeeded in quite disposing of nervous structures as a factor in autonomy of the heart. The development of research to the present time shows a tendency to reconcile the two views. We are indebted to the champions of the myogenic theory for the most complete analyses of the direction of the nervous system over the rate and rhythm of heart beat. The cardiac nerve supply is composed of centripetal and centrifugal paths. All of the known paths are centrifugal with the exception of the depressor, which is centripetal and has its reflex arc through the vagus. The accelerator centres have been located in the medulla and the accelerator and inhibitory impulses come through the sympathetic and vagus centrifugal paths respectively.

The question of the rôle of Remak's, Biedert's, and Ludwig's ganglia in the automatic rhythm and correlation of function of the chambers of the heart is one which will necessarily interest the student who wishes to consider forms of cardiac arhythmia. Whether the ganglia are responsible for transmission of impulses within the heart and whether they control a reciprocal action of auricle and ventricle with the significance of nerve centres or whether they are terminal structures through which the reflex control of the heart is maintained is an unsolved problem. The champions of the myogenic theory have adopted a nomenclature for certain modifications of cardiac activity which is employed to great advantage in classifying some of the disturbances of rate and rhythm of the heart. This very minute direction of the heart by nerve agency has been classified into chronotropic, inotropic, dromotropic, and bathmotropic influences. In the present state of our knowledge of the mechanism

of these influences, they have for the clinican a purely symptomatic and not an anatomical significance. The chronotropic influences are all those which modify the rate of the heart; the positive chronotropic influences increase the rate and the negative chronotropic influences diminish it. Positive inotropic influences increase the force and excursion of the heart muscle in its action and negative inotropic influences diminish its force and excursion. Dromotropic influences are those which modify the transmission of muscular waves within the heart. Positive dromotropic influences facilitate the transmission of waves and negative dromotropic influences retard the transmission of muscular waves. Positive bathmotropic influences increase the sensitiveness of the myocardium in response to stimuli, that is, a positive bathmotropic influence will render the heart susceptible to a stimulus of lesser intensity and a negative bathmotropic influence renders the heart less susceptible to stimuli. Although the myocardium may enjoy an autonomy independent of its nerve supply, we see the work of the heart in its minutest detail is assigned to the direction of the nervous system. It is very desirable in clinical study to locate the source of these influences in the myocardium, extracardial nerves, the basal ganglia, the cerebral cortex, or remote nerve terminations in the abdominal and pelvic sympathetic distribution. For clinical consideration we still accept a purely symptomatic classification of tachycardia, bradycardia, and arhythmia.

TACHYCARDIA.

An increase in the heart rate may occur in some stages of the progress of nearly all pathological processes; in the usual form of rapid heart or polysystole the increase in the rate is accomplished at the expense of diastolic time in the cardiac cycle. The long pause is much shortened, but the shortening of time between the systolic and diastolic sounds is not apparent. We may have a great increase in the heart rate, but on auscultation we are able to differentiate phases of the cardiac cycle by the intrinsic character of the two sounds and spacing of the silent phases. By *embryocardia* we understand not only an increase in the heart rate, but also a modification of the heart sounds and spacing of the silent phases. In embryocardia the systolic and diastolic sounds are identical in character and there is a shortening not only of the long pause, but also of the short pause, and the two have the same length. This condition in the heart is analogous to a vasomotor disturbance in the arterial pulse. Embryocardia is to the heart what pulsus parvus et celer of vasomotor exhaustion is to the artery. If this is a legitimate physiological conception of the heart's action the term tachycardia is very suitable for this phenomenon. The distinction between polysystole and embryocardia is very clearly brought out in instances of rapid heart rate, such as we may see in pressure neuritis of the vagus on which is grafted the phenomenon of paroxysmal tachycardia. So long as the heart's rate is maintained at 140 or 160 we are able to identify the phases of the heart sounds by their character and by the spacing of the silent phases. If an attack of paroxysmal tachycardia should appear, all this differentiation

is effaced and we have the phenomenon of embryocardia. For the production of embryocardia we must have a marked shortening of the refractory period of the systolic phase of the heart and shortening of the compensatory pause. Thus we see tachycardia with embryocardia exhibits phenomena which correspond to a prolonged series of extrasystoles.

Medical writers have endeavored to differentiate between primary or essential tachycardia and reflex tachycardia. If we use the term *reflex* as our knowledge of physiology of the cardiac nerve supply will permit, it is possible in the writer's experience to find few cases of paroxysmal tachycardia which were not reflex in origin. We must conceive all influences from the cortex of the brain as reflex as well as influences which come from the distant systemic nerve supply. Paroxysmal tachycardia is clinically inseparable from embryocardia. The duration of attacks varies from a few minutes to two months. The onset is sudden and the termination is equally abrupt. The patient will often have a premonition of impending tachycardia by an occasional extrasystole or intermission. These occasional warnings may occur over a period varying from a half-day to a few minutes, but paroxysms often begin without the slightest premonition. The onset is characterized by subjective symptoms which accompany a vagus pulse. There is a feeling of oppression over the precordial area, a sense of numbness and weakness in the left arm, a feeling which is described as a sudden flow of blood to the head, and then a throbbing feeling over the heart. The patient feels his pulse and finds a furious tachycardia has commenced. The manner of onset and cessation is very sudden in all cases of tachycardia which we can conceive as having their origin in the medulla. A gradual abatement does not characterize tachycardia which is myocardial in origin. Even where vagus pressure is the cause of tachycardia and rapid heart rate is constant throughout the course of the disease, we may have paroxysmal attacks which are analogous to the crises in diseases of the central nervous system, such as tabes. The case of spasmodic asthma in the child with tuberculous mediastinal glands may be regarded as a pulmonary crisis of vagus disease. Cardiac crisis in the course of vagus disease is a closely related conception. Two cases of paroxysmal tachycardia, both of which occurred in physicians, elucidate this point. One occurred in a man who in every other respect was perfectly healthy. There was no suspicion of any organic or functional disorder. The other occurred in a man who had tuberculosis in both lungs with enlarged tuberculous mediastinal glands and tuberculosis of the genito-urinary tract. This man conducted an office consultation practice, and at times was interrupted in his work by paroxysms of tachycardia which recurred at intervals from one to two months. He would retire to a private room and with the aid of an assistant stand on his head. The tachycardia ceased a few moments after he was inverted. The first patient adopted the same practice and found the attacks ceased directly he was in the inverted position. Both were relieved by the same procedure, although one had gross pathological lesions in the mediastinum and the other was free from any pathological signs. If there is any method of differentiating between a myocardial or essential tachycardia

and one which has its origin in the central nervous system, it is the therapeutic test. If tachycardia can be allayed by stimulating the vagus trunk or by exciting the medullary inhibitory centre, then the source cannot be in the myocardium. If these measures are futile, the evidence goes to show that the abnormal stimuli originate in the myocardium.

Nothnagel conceived the cause of paroxysmal tachycardia as analogous to the nervous state in petit mal and epilepsy. He regarded the attack as being a temporary slumber of the vagus centre. Cases which are relieved by measures which affect the vagus centre are quite consistent with this conception. It is impossible to reproduce the picture of tachycardia by any experimental procedure on the vagus or the accelerator. It seems as though the symptoms of paroxysmal tachycardia must have their origin in some molecular change within the medulla. Frequently the attacks are accompanied by other bulbar symptoms, such as spasm of the glottis, stridulous respiration, dilatation or contraction of the pupils, polyuria, and sweating, Vomiting may occur either during the attack or at its conclusion. Rose[1] described a patient whose attacks lasted a week or more. The approach of the end of an attack was always preceded by a herpes labialis on one side.

During the attacks of tachycardia the precordial region is moderately sensitive. The arms feel heavy, and although the sense of exhaustion is only moderate in the beginning of an attack, there is always a strong impulse to occupy a horizontal position. The signs of stasis do not appear early in an attack, rarely in the first twenty-four hours; but if the attack is prolonged we may have the complete picture of myocardial failure, dilatation of the heart, distended veins, pulmonary stasis with albuminous or bloody expectoration, hepatic enlargement, albuminuria, œdema of the legs, and cyanosis. Cases which present all of this train of symptoms corresponded to Bouveret's conception of essential paroxysmal tachycardia, and although the duration of life may be very many years, death ultimately comes in the course of an atack of tachycardia.

One patient with associated myocarditis experienced great discomfort from palpitation, with a heart rate of 140 after moderate exercise; but during the paroxysms of tachycardia with a heart rate of 220 there was not the slightest subjective palpitation. The sense of palpitation is dependent on hyperdiastole, not on the rate of contraction. These patients may have vascular palpitation, which is determined by the rise and celerity of the pulse wave. The pulse may be of the celer type with considerable excursions of the artery. It may be hyperdicrotic or extremely small and monocrotic. These deviations in the character of the pulse depend upon the dilatation of the splanchnic vessels and the volume of the pulse wave. The patient may be flushed or pale, depending entirely upon the relative distribution of the blood to the periphery and splanchnic area. Cyanosis is pronounced in the prolonged attacks accompanied by failure of the blood hydraulics.

Treatment.—Treatment of the individual attacks is directed either toward stimulation of the vagus, stimulation of the inhibitory centres, or

[1] *Berlin. klin. Wochenscrift*, 1901, Nrs. 27 and 26.

modifying the blood distribution by employing pressure or the aid of gravity to empty the splanchnic veins. The vagus may be stimulated either by direct compression or by the galvanic current. Bulbar stimulation may be attempted by the use of a spray of ether or ethyl chloride over the nape of the neck. By placing the patient with the head and trunk downward we not only drain the splanchnic regions, but produce a passive hyperemia at the base of the brain and thus stimulate the vagus centre. Compression of the abdomen has been employed successfully by wrapping a towel tightly about the abdomen. In this manner uniform and strong pressure was exerted on all sides of the abdominal cavity. Patients frequently find they can stop the attacks if they take a deep breath, close the glottis, and make a strong expiratory effort while lying down with the head low. By this method they accomplish the very results which are attained by the inverted position or abdominal compression. Local application of ice-bags and leeches over the precordial area seem to be of little or no service, although commonly employed. Drugs are of very doubtful value and various men report success with drugs which cause vascular contraction and drugs which cause vascular dilatation. Quinine in large doses, ergot, and adrenalin are of the first class. Nitrite of amyl and nitroglycerin have been employed in the second class. Digitalis seems the most rational drug to employ when the mechanical therapy above described fails to give relief.

BRADYCARDIA.

The frequency of bradycardia varies greatly in the experience of physicians; from 4 to 17 per cent. of the total number of patients are reported by different men. Some writers report bradycardia as more common in men than in women. From reports of various writers the proportion of women to men is all the way from 6 to 50 per cent. Bradycardia may result from reflex and direct stimulation of the vagus centre, from irritation of the vagus trunk, or it may originate in the heart itself. An approximate differentiation between these various sources of bradycardia may be shown by the employment of atropine, which paralyzes the vagus terminations in the heart. Given a case of bradycardia which will show a marked increase of the heart rate after the administration of atropine, we can assume the cause of bradycardia is extracardial. Intracardial bradycardia may be slightly affected by atropine if the normal negative dromotropic influence is intact. From experience, however, we find bradycardia associated with myocarditis is little affected by atropine. In the Stokes-Adams syndrome a combination of the myocardial and extracardial causes may exist. Sclerosis of the coronary arteries and the bulbar vessels may give the negative dromotropic effects at the atrio-ventricular bridge (heart-block) and stimulation of the medulla from anemia.

Bradycardia which accompanies acute infections may have two sources of origin—namely, myocarditis and infectious vagus neuritis. *Myocardial* bradycardia may be due to negative bathmotropic influences from muscular exhaustion or it may be caused by negative bathmotropic

influences due to the effect of some toxin at Remak's ganglia. Negative dromotropic influences may also cause a slow pulse if there be poor muscular nutrition, degenerative myocarditis, or toxic effects on the heart muscle. Negative dromotropic influences resulting in heart-block may be myogenic or neurogenic in origin. The mere existence of heart-block does not exclude a possible vagus origin of bradycardia. Atropine when given in considerable doses to young and vigorous persons will increase the heart rate from 20 to 50 beats in a minute. When given to older persons the increase in the heart rate is not so pronounced. This does not necessarily imply a loss of efficiency in the myocardium, but a diminution of irritability. Bradycardia due to heart-block at the atrioventricular bridge will not be affected by atropine. In such an instance the automatic rhythm will be perfectly normal at the auricle, but transmission to the ventricle is impaired. Atropine, therefore, may not affect ventricular bradycardia if the automatic rhythm of the auricle is normal. It is conceivable that atropine may be of some service in forms of myocardial bradycardia by diminishing the vagus-negative dromotropic influence. Therefore, atropine cannot be dogmatically forbidden in myocardial bradycardia. Given a case of slow pulse one must not only take the precaution to determine if the number of heart beats coincides with the pulse, but also, if possible, whether there may not be two or more contractions of the auricle to one of the ventricle. In many instances of rhythmic bradycardia we see in the external jugular vein, or bulbus venosus, centrifugal pulses which betray two or three contractions of the auricle to one of the ventricle. Many of the most pronounced cases of bradycardia with a heart rate of 16 or 18 to the minute have occurred in disease of the coronary arteries. These are the very cases in which conditions are most favorable to heart-block and many of these are merely ventricular bradycardia from heart-block and are not bradycardia from negative bathmotropic influences. Under the latter conditions there will be an absence of signs in the jugular veins.

Bradycardia originating from the central nervous system is in most instances *reflex* as well as that which originates reflexly from more remote nerve distribution. A few exceptions are cases caused by bacterial emboli in the medullary vessels, disease of the vessels supplying the medulla and bulbar affections in diseases of the cord and brain. Any process which causes an increased intracranial pressure may cause bradycardia. Bradycardia may occur in melancholia, hysteria, and neurasthenia, and is sometimes found in syringomyelia, combined systemic disease of the cord, and tabes dorsalis. Bradycardia may also occur from pressure on the cervical cord due to neoplasm, hemorrhage, or disease of the vertebræ. Van Noorden reports 11 cases of hysteria and neurasthenia, in 6 of which there were symptoms from the stomach or larynx with bradycardia. Wallenberg reports a case of bradycardia which was apparently due to severing the accelerator fibres leading to the sympathetic from the third dorsal nerve. A policeman while making an arrest received a stab wound on the left of the third dorsal vertebra. Directly on receiving the injury, he observed there was something wrong with his heart. He had anesthesia in the regions supplied by the

third dorsal nerve and bradycardia which ceased with healing of the wound.

The writer saw, with E. Carter, of Cleveland, a young, vigorous man suffering with a recurrence of rheumatic fever. The right knee-joint was distended with fluid but not painful. With the second attack there was no elevation of temperature. Simultaneous with the return of arthritis in the knee-joint, an acute phlebitis of the right femoral vein developed, which apparently involved the venous trunk above Poupart's ligament. There was intense pain over Scarpa's triangle and deep in the right inguinal region above the bend of the thigh. While this pain was at its height the patient developed a bradycardia of 30 per minute, with arhythmia. The arterial pressure was low and there was no discomfort referred to the precordial region. There was no dyspnœa, cough, or pain in the thorax and no subsequent subjective or objective signs of pulmonary infarct. In the absence of all signs of pulmonary or crossed emboli the only explanation was reflex vagus inhibition through the abdominal sympathetic from branches of the superior hypogastric plexus. The bradycardia persisted for about ten hours. The heart rate gradually increased to 70 in the course of a few hours and remained so during convalescence. There was no recurrence of pain after the bradycardia ceased. The thickening of the femoral vein was distinctly palpable. This explanation is not far-fetched, if we consider that cardiac inhibition results from stimulation of the central end of the splanchnic and the observations referred to by Kisch, who cites instances of sudden death which occurred during parturition and slight operations on the genitalia. Hegar (cited by Kisch) observed that slowing and arrest of the heart beat were caused by pulling on the ovaries and by removing them. The path of reflex inhibition suggested by Kisch is through the abdominal sympathetic by way of the superior hypogastric plexus. My colleague, Hunter Robb, has had several experiences which go to confirm this reflex path for the production of bradycardia. After abdominal section and operation on the Fallopian tubes he observed bradycardia as low as 20 per minute in several patients.

Bradycardia from the *vagus* trunk may occur with hemorrhage in the vagus sheath, pressure from primary or secondary growths, and inflammation of the vagus in multiple neuritis or vagus neuritis from toxic sources, *e. g.*, lead poisoning and the vagus neuritis which follows the acute infections, of which diphtheria and influenza are the most frequent. A vigorous young workingman, aged twenty-two years, gave a history of slight chill with fever and headache for several days before the following symptoms appeared. About four days after the fever subsided he was seized with severe pain in both sides of the neck, which was referred along the sternomastoid muscle; rotation of the head and bending the head to either side caused severe pain. Though he was going about the heart was arhythmic and had a rate of 60. The heart was not dilated and the patient was not dyspnœic. The heart sounds were clear, but there was a distinct lengthening of the short pause and the aortic closure was accentuated. Moderate pressure over the vagus at the middle of the anterior border of the sternomastoid muscles on both sides slowed

the heart rate to 30 per minute and increased the arhythmia. The pupils were equal and reacted normally to light and accommodation. There were no other signs of disturbed vagus innervation. The symptoms all disappeared in about two weeks' time.

FIG. 15

Tracing from the radial artery.

This tracing from the radial artery was procured from a man with diabetes mellitus, moderate arterial sclerosis, and a history of syphilitic infection twenty-five years ago. The sudden intermission and subsequent slowing of the heart rate was caused by giving him a single short dig with the finger over the site of his vagus trunk in front of the middle of the sternomastoid muscle of the right side. Firm pressure over this site caused such cardiac inhibition that it seemed dangerous to employ prolonged pressure. After treatment for both diabetes and syphilis which was used for several months, the vagus no longer responded in this manner. This was probably a diabetic neuritis of the right vagus nerve. All cases of vagus neuritis do not respond to mechanical irritation; this probably depends on the portion of the vagus involved.

Huchard cites a case of bradycardia in pericarditis described by Graves, in which the heart rate was reduced to 36 per minute. There are two sources for such a bradycardia. It may originate from vagus neuritis secondary to mediastinitis or from myocarditis secondary to epicardial inflammation. Neusser reports a case of bradycardia which was attended with acetonuria and strongly simulated meningitis. The bradycardia promptly disappeared after liberal doses of calomel. Bradycardia may occur in a number of intoxications, such as by lead, digitalis, muscarin, picric acid, and physostigmine. Nicotine in pharmacological experiment is found to slow the rate of the heart, but we do not see this phase of nicotine poisoning in smokers, as the patient does not consult his physician until the later effects of rapid heart and arhythmia appear. In the course of infectious disease there are several sources of bradycardia to be considered: the infectious vagus neuritis, myocarditis, and toxins which may affect the heart muscle or its nerve supply. Roger described endotoxins in bacteria which caused a slowing of the heart rate and dilatation of the splanchnic vessels, results similar to those attending irritation of the depressor nerve of the heart. The diagnosis of bradycardia requires first to determine the relation of the arterial pulse to the number of heart impulses and the number of centrifugal pulses in the vein. To learn whether there is a genuine bradycardia, ineffectual heart beats or heart-block, the next procedure will be to look for evidence of disease in the brain or spinal cord and any possible sources for toxic

infections or pressure vagus neuritis, and finally we must consider the myocardium and seek for possible sources of reflex stimuli.

The feeling of palpitation in bradycardia may be a very uncomfortable symptom if there is hyperdiastole. If there is no hyperdiastole the patient will discover his bradycardia only on account of some cause other than the heart rate which leads to an examination of the pulse. The mere slowing of the heart rate is well tolerated. Subjective or objective signs are due to other causes than the mere bradycardia.

Treatment.—The treatment of any case of bradycardia depends upon its origin. If the ultimate cause cannot be determined, the treatment must be purely symptomatic. If the pulse shows a considerable degree of peripheral resistance, the employment of nitrites in the form of sodium nitrite, nitroglycerin, and nitrite of amyl may cause the symptom to disappear by improving the blood supply to the coronary distribution and the medulla. Atropine will increase the pulse rate if there is a genuine bradycardia due to direct or reflex vagus excitation. When the slow pulse rate is due to heart-block, atropine will increase the rate of auricular systole, but the rate of ventricular systole is unaffected. This does not invariably follow, so a trial of atropine is justifiable in bradycardia from any cause. Warm applications should be employed when the surface of the body and extremities are cool. The limbs should be elevated and the head lowered to combat cerebral anemia. If atropine and the nitrites are not effective, caffeine in liberal doses hypodermically may be employed. Drinking hot coffee may also be of service.

CARDIAC ARHYTHMIA.

Cardiac arhythmia is so protean in its character and method of origin and varies so widely in prognostic and diagnostic significance, that there can be no fixed plan for interpreting its meaning. Any form of arhythmia must be considered in its broadest pathological and etiological relations, before its real portent can be understood. Any disturbance of the heart's rhythm is liable to bring its activity within the consciousness of the individual which is always uncomfortable and often terrifying. Whether or not the patient is conscious of his arhythmia seems to sustain no constant relation to the habit of introspection. Some patients who are very much occupied with their own sensorium are quite oblivious to a degree of arhythmia which in other persons causes great alarm. This may, however, depend upon the points to which the patient's attention is directed. The physician's diagnostic art is rarely more severely taxed than in explaining the cause and significance of some cases of arhythmia. It may be due to stimuli of many kinds from the meninges, cerebral cortex, base of the brain and cord. Arhythmia may be a conspicuous sign when there is irritation in the vast region supplied by the great thoracic abdominal and hypogastric sympathetic chain and finally the heart itself or its direct nerve supply may be the sources. This very large range of possibilities brings the clinical study of cardiac arhythmia in touch with the whole field of pathological physiology.

Another feature of the mechanism of arhythmia still further compli-

cates its study, and that is the varying results to the heart's rhythm which are obtained both clinically and experimentally at various times by what seem to be identical conditions. Cardiac activity is the expression of coördinate excitation and inhibition in the nerve paths and nerve centres, and when we consider the close anatomical relation of excitory and inhibitory paths and centres and the equilibrium of the automatic centre in the heart itself with the property of the auricle and ventricle to independently assume the rhythm, then we have some conception of the very intricate problem. To appreciate this phase of the subject we have only to read the conflicting reports from experimental studies of vagus influences. Reflex influences on the heart rhythm from every source may at different times have different effects. Myocarditis may increase or diminish the heart rate or cause it to be irregular. Pressure on the vagi from tuberculous disease of the mediastinal glands has been observed to cause paroxysmal bradycardia and paroxysmal tachycardia. Gaseous distension of the stomach may cause genuine bradycardia, heart-block, tachycardia, extrasystole, genuine arhythmia, and the cycle of vagus irritation. These signs may occur in the same person at different times and in the same attack a transition from tachycardia to bradycardia with heart-block has been seen.

Besides these factors we must consider the share that psychic stimuli contribute to the production of arhythmia. Nervous persons who occupy themselves with the study of their pulse are able to produce arhythmia. Psychical arhythmia is seen in hysterical and hypochrondriacal patients to persist continuously, and during periods of great mental or emotional distress arhythmia has been observed to be paroxysmal, just as rapid heart and slow heart are commonly seen to assume the paroxysmal character. Mental impressions which are severe although not protracted, and are unassociated with injury or bodily suffering, may be responsible for cardiac intermissions for months afterward. This form of arhythmia is frequently submitted to the physician's judgment in traumatic neuroses which involve a claim for damages. Cardiac arhythmia occurs under these conditions when there is no claim for damages to modify the course of the affection. Meningeal irritation of the early stages of tuberculous meningitis in children is commonly associated with arhythmia and believed to have diagnostic importance in the early stages of vomiting, but slow heart rate and arhythmia may be caused by reflex vagus irritation in vomiting from any cause. Irritation of the vagus trunk may cause arhythmia, but in such cases it is associated with a diminution or increase in the heart rate. Arhythmia from this source accompanies diseases in the mediastinum and toxic effects on the vagi and infectious inflammations of the vagi. Heubner reported several cases of arhythmia in children following the use of digitalis and opium in small therapeutic doses. Tea and coffee are credited with causing arhythmia, and the writer has had several patients in whom tea and coffee were apparently the cause of moderate arhythmia; at least the arhythmia ceased after coffee was discontinued. Immoderate drinking of tea and coffee certainly has decided effects on the vasomotor system and increases the force and frequency of the heart beat, and possibly

even in small amounts causes arhythmia in susceptible persons. A conclusion in this matter is not justified unless the patient is under observation for a long period and there is opportunity to see how the heart's action is affected by alternately using and quitting tea and coffee.

Reflex stimulation of the vagus nuclei is apparently the cause of arhythmia in affections which involve the region supplied by the great abdominal sympathetic chain and its branches. Huchard reports one case of arhythmia which persisted for three years and was cured directly after a polyp was removed from the uterine cervix. Arhythmia is frequently seen in the postcritical period of acute infectious diseases and is more commonly seen in cases which terminate in crisis than in those which terminate by lysis. This may be caused by toxic effects or by an infectious myocarditis; which is responsible in a case lasting a short period it is impossible to determine. It is only in cases which last a long time and subsequently show signs of myocardial dilatation that we can differentiate between these two causes. Up to the present time there have not been a sufficient number of cases studied to show the relation between various forms of myocardial disease and certain forms of arhythmia. That disease of the atrioventricular bridge will cause heart-block is clearly shown, but beyond this no one has satisfactorily proved that disease of certain portions of the auricle or ventricle have any specific association with disturbances of rate or rhythm of the heart beat. There are cases of marked and constant arhythmia which have been known to exist for many years without causing any functional impairment of the heart's work. Huchard reports three such cases which persisted from childhood to advanced life and Da Costa reported one case which was seen in the twenty-first year of life and was first recognized when the patient was six years of age. The writer knows one man, aged forty years, who has a very irregular heart rhythm which was accidently discovered when he was eighteen years of age. During the past twenty-two years the arhythmia has not varied; there are no other abnormal signs in the the heart or circulatory system, and he has conducted a business which requires considerable exertion without the least discomfort. Even when arhythmia accompanies acquired heart lesions, patients learn after a time to exclude the arhythmia from their consciousness. The heart-flop, which at first is distressing and alarming, escapes perception after the symptom has lasted for some months. Extrasystole is the form of arhythmia which is most perceived over the heart's region. Genuine arhythmia such as occurs after an infectious disease like influenza is commonly imperceptible to the patient. One patient described two sorts of experiences associated with arhythmia: "One when I feel my heart flop or turn over, and the other is when I notice nothing about my heart, but suddenly start to fall and feel as though I were losing consciousness, when my heart gives a sudden throb and catches me before I lose my footing." The latter experience was due either to a genuine intermission or an extrasystole very early in the diastolic phase and followed by a long compensatory pause.

It would be a valuable aid to the clinical and pathological interpretation of various forms of arhythmia if we were able to differentiate between

genuine arhythmia, heart-block, and extrasystole in which the rhythm is assumed by the auricle, and those in which the extrasystole is assumed by the ventricle, but there are several difficulties in the way which thus far have not been satisfactorily solved. Studies of comparative tracings of the venous and arterial pulses and precordial impulses have contributed greatly to our interpretations of arhythmia, but further observations are needed before we can arrive at definite conclusions. Precordial impulses are very misleading if we use their tracings to mark the phases of a cardiac cycle, and the difficulty in getting reliable results from tracings of the internal jugular pulses is equally great. The method employed fails to eliminate the factor of centripetal pulses in the internal jugular vein and only partially solves the problem of eliminating from venous tracings the communicated impulses from the carotid artery. In cases of heart-block where there is great dilatation of the jugular veins and the external jugular pulses are clearly free from a centripetal flow and communicated impulses from the internal jugular and carotid artery, such tracings are successfully made, but finer analyses of these phenomena at the bedside have thus far failed to give completely satisfactory data from which to interpret the various forms of arhythmia.

Treatment.—The treatment of arhythymia as a symptom will depend entirely on the underlying cause. When caused by negative dromotropic influences from vagus excitation atropine will serve to increase the heart rate and restore the rhythm, or in certain cases a diminution of the normal vagus tone by the effects of atropine may serve the same purpose. In heart-block due to disease of the atrioventricular bridge, atropine will increase the rate of the auricle, but will not affect the ventricular rhythm. Digitalis is efficient in restoring the rhythm of the failing myocardium with rapid rate, but our analyses of the subject have thus far offered no further therapeutic indications in its employment to affect the heart rhythm. Cardiac arhythmia caused by some reflex stimuli should be treated by seeking the original cause of irritation.

ANGINA PECTORIS.

Angina pectoris, a disease associated with general and regional vasomotor crises and with nutritive and functional ischemia of the myocardium, has received as many explanations as there are concomitant symptoms accompanying the attacks. For instance, one writer speaks of Cheyne-Stokes breathing as a symptom which characterizes some attacks of grave angina pectoris. Biot's and Cheyne-Stokes type of respiration may accompany angina pectoris, but there is no interdependence between the cardiac and sensory phenomena and respiratory phenomena. The angina is dependent on disease in the coronary arterial distribution, and the respiratory phenomena are dependent on disease in the arterial distribution to the base of the brain. The respiratory and cardiac symptoms are separate and regional manifestations of the same systemic arterial disease. They are merely concomitant symptoms, and sustain no causal relation to each other.

Another writer wishes to create a class of angina pectoris which is char-

acterized by signs of engorgement in the pulmonary vascular system, a symptom dependent on the accompanying myocardial disease but not characteristic of angina pectoris. Huchard collected all the explanations which have been offered, and finds as many as eighty.

Angina is associated with an impairment of the blood irrigation of the myocardium. This can arise in several ways:

1. Isolated disease of the coronary arteries unassociated with any affection of the aorta, aortic valves, or systemic arteries.

2. Disease of the coronary arteries associated with systemic arterial disease.

3. Partial or complete occlusion of the lumen of the coronary arteries at their origin on account of disease of the aortic valves or disease of the root of the aorta.

4. Vascular crises in the coronary arterial distribution due to vasomotor influences not associated with anatomical lesions of the arteries.

The resourcefulness of the myocardium in meeting sudden demands upon its reserve energy requires great fluctuations in its blood supply. This wavering blood supply can be secured only by actively varying vasomotor activity. Moreover, the myocardium shares with the gray matter of the central nervous system the highest degree of sensitiveness to an impaired supply of oxygen. From the above classifications there is opportunity for widely differing pictures of angina. An instance of the first class was observed in a man aged sixty years, who had only three attacks of angina prior to his final attack. These occurred at intervals of about six months, and were accompanied by violent pain in the precordial region and dyspnœa. All the attacks followed upon physical exertion. The third attack of pain preceded his sudden death by six months. At the autopsy the heart muscle valves, aorta and its branches showed no signs of disease. Both coronary arteries were normal throughout their entire length, with the exception of three-quarters of an inch on the left coronary at the upper portion of the anterior interventricular groove, where the branch of the artery was calcareous and the very small lumen was obstructed by a fresh thrombus. There were no traces of old infarcts in the myocardium. In such a case we have to deal with a functional ischemia prior to the final attack.

The patient with a sclerosed coronary artery as above described suffers from functional ischemia for several years, and finally (with complete obstruction of the coronary artery) a nutritive ischemia ensues over a sufficiently large portion of the heart to cause death. These patients have no increased arterial pressure during their attacks. Vasomotor factors do not share in the production of the symptoms, but their pain is dependent directly on exercise, and can invariably be produced by exercise. Such an angina has a graver significance and demands a more cautious prognosis than the angina which occurs in a patient suffering from general arterial sclerosis and vasomotor spasms.

Angina due to coronary disease without signs of diffuse arterial sclerosis may be very misleading and tempt the physician to underestimate the gravity of the symptoms. The patient's color may not change, there will be no signs of an increased vasomotor resistance, the pulse will show only

an increase in rate and lowered pressure, and there may be no disturbance in rhythm. The writer has observed several such cases. The patients were advanced in years and gave a history of having suffered several attacks of pain during the week preceding sudden death. These old people suffered what they believed to be "an attack of wind on the stomach." Indeed, from their conduct one would not believe they suffered intense pain. One old man suffered several attacks of pain during the few days preceding sudden death, but continued to wander about the infirmary halls until the evening he suddenly expired. The autopsy revealed a myomalacia cordis with rupture of the heart wall and several anemic infarcts in the vicinity of the softened area. Several such experiences led the writer to suspect that these old people tolerate grave lesions of the myocardium better than younger or more vigorous persons, just as gall-stones and renal calculi cause less suffering in the old and feeble than they cause in younger and vigorous subjects.

When disease of the coronary arteries is associated with diffuse arterial sclerosis it is common to see very severe systemic vasomotor spasm accompany the attacks of pain, but the pain is apparently not caused by the increased resistance to the heart's work, but because the coronary arteries share in the vasomotor spasm. In the Lakeside Hospital, Cleveland, we had such a patient whose arterial pressure ordinarily was 180 mm. Hg. During his attacks of pain the pressure repeatedly rose to 300 mm. Hg. The arterial tension and the pain would subside after the administration of large doses of nitroglycerin. Death was not caused by angina pectoris, but by renal insufficiency. The autopsy revealed marked sclerosis throughout both coronary arteries, but there were no traces of myocardial infarct and no thrombi in the coronary arteries. All these points contribute to the proof of a systemic vasomotor-arterial spasm which was shared by the coronary arteries.

Occlusion of the coronary arteries in disease of the aortic walls and aortic valves is a relatively uncommon form of angina.

A patient seen by the writer twelve years ago in several attacks of angina is still living in a tolerable state of comfort. This patient had an old endocarditis which involved both the aortic and mitral valves. During one attack the arterial pulse became arhythmic and very slow, twenty to the minute. During the bradycardia with arhythmia the jugular veins were distended and pulsated very rapidly. The relative rate of pulsation in the veins and the arteries was not noted at the time, but the slow arhythmic, full arterial pulse and the dilated, rapidly pulsating jugular veins were noted. Reviewing the case today, it seems certain that there must have been an acute heart-block with the attack of angina. The results of an embolus in the coronary arteries will vary, of course, with the tolerance of the affected myocardial zone. Should the atrioventricular bridge be included in an area of transient ischemia of the myocardium, then heart-block would be coincident with angina.

Merely high aortic pressure is not sufficient to cause precordial pain. We occasionally see patients with arterial sclerosis who have a systolic blood pressure not far from 300 mm. Hg., but they are quite comfortable so long as they remain at rest. One patient with general arterial sclerosis

occasionally has arterial crises without pain, but in these attacks we must assume the coronary arteries are not included in the vascular crises. Such vascular crises are probably responsible for *angina sine dolore,* which is described by some authors as occurring in the course of cardiovascular disease.

Angina of *vasomotor* origin without anatomical disease of the arteries is reported as a result of the abuse of tobacco, and of neuropathic origin. The writer has never witnessed an attack of the kind, but from regional vascular crises in the cerebral, retinal, and brachial arteries one is disposed to credit such an interpretation.

The terms "false" and "true" angina pectoris are unfortunate. The patient who has the symptoms of angina from vascular crises suffers from as true an angina as the patient whose angina is caused by sclerosis of the coronary arteries. The difference lies in the pathological anatomy of the two kinds of angina, but the physiological pathology of the two is the same. In both instances we are dealing with myocardial ischemia.

Patients suffering from cardiovascular disease with attacks of angina usually present several points of tenderness to pressure; the site of the spinal accessory as it turns over the sternocleidomastoid muscle, the second and third ribs about an inch external to the left sternal border, are the most common points of pressure tenderness. When there is aortitis, the second right interspace at the sternal border is sensitive to pressure, and in many instances the apex of the heart is markedly so. The *subjective pain* of angina pectoris may have a very wide distribution, the lower end of the sternum usually marks the site of most intense pain, but it may be over the precordial area to the left of the sternum. The pain may extend into the side of the neck over the distribution of the third cervical segment. In the arm the area of pain is most commonly in the distribution of the eighth cervical and first, second, and third dorsal segments.

Epigastric pain and vomiting are very common in angina from myocardial infarcts, but it is very probable that the gastric symptoms described in some cases have been caused by disease of the arterial supply to the stomach, and not to referred pains from the heart. In the past there has not been sufficient appreciation of the rôle of vascular crises and functional and nutritive ischemia due to disease of the branches of the abdominal aorta and to disease of the arteries to the brain, so that the respiratory and nervous symptoms and symptoms from the abdominal viscera which have been so closely linked with attacks of angina pectoris are merely concomitant and do not sustain an essential relation to cardiac angina.

Treatment.—This will depend on the presence or absence of vascular signs during the attack. If there is high arterial pressure, nitroglycerin should first be tried in drop doses of a 1 per cent. solution placed on the tongue. The drop should be repeated every minute until the arterial tension is lowered or the characteristic discomfort from use of the drug prevents its further use. Some patients require as much as ten or even twenty drops before the arterial pressure is lowered. If the tension cannot be lowered by nitroglycerin on account of intolerance of the drug in sufficient doses then nitrite of amyl should be given by inhalation; some patients tolerate it much better than nitroglycerin. Inhalation of chloro-

form is often helpful in severe attacks. If the attack of pain is not accompanied by signs of vasomotor spasm, hypodermic injections of morphine should be employed without delay. In patients who have had a syphilitic infection, iodide of potash and mercury are, of course, indicated to give relief from syphilitic arteritis of the coronary arteries. But in coronary arterial disease of the senile type, iodide of potash in doses of 5 grains or less should be persistently employed.

"Pseudoangina"—This is a term used to describe attacks of cardiac pain unassociated with pathological lesions of the myocardium, coronary arteries, or aorta. The term is unsatisfactory because the pathological physiology of false angina is not clearly differentiated from the pathological physiology of true angina. The postmortem demonstration of sclerosis of the coronary arteries with thrombi and secondary disease of the myocardium satisfies the inquiring clinician at the autopsy table, but it does not explain all the phenomena encountered in repeated attacks of angina during a long clinical history. There are several possible sources for the pains of angina, and one of them is spasm of the coronary arteries. The plausibility of this source is supported by the frequent association between angina and vascular spasm elsewhere in the aortic distribution, and the occasional death from angina pectoris when we are compelled by exclusion to employ this explanation for a lethal termination. The phenomenon of vascular crisis in various parts of the body is associated with such grave and palpable results that we can readily imagine the results of a crisis in the vascular supply to the myocardium. Intermittent claudication and cerebral signs, both general and focal in character, are not uncommon in the clinical course of arterial sclerosis. There is nothing in the line of a vascular crisis, however, which brings the nature of the process so clearly to our vision as spasm of the retinal arteries accompanied by amaurosis. Regional vascular crises in the veins as well as the arteries are seen as a rare accompaniment of brain tumors and brain syphilis. This very striking clinical symptom, once observed by the writer in the left arm of a patient suffering from brain syphilis, could be well described as a brachial angina. Vascular crisis in the splanchnic vessels in tabetic patients and those suffering from lead poisoning, albuminuria of vasomotor origin in severe mental excitement, all contribute to give to the so-called pseudoangina or angina vasomotoria a significance which implies grave possible results to an organ so dependent on a blood supply for its function.

We occasionally meet with cases of angina which have all the characteristics of true angina in the manner of onset, distribution of pain and dyspnœa, and yet these patients some years later are able to perform severe physical labor without discomfort and are quite free from their old complaint. Such cases present all the signs which satisfy a diagnosis of true angina. The patient is seized with violent pain over the sternum and heart area to the left of the sternum. They describe the pain as a violent constricting pain which compels them to remain quiet until it subsides. Dyspnœa is very pronounced and the pain may radiate into the arm and shoulder, just as in true angina from disease of the coronary arteries and the aorta. With the employment of cathartics to combat constipation, which may often be the cause of the difficulty, the attacks cease. It seems

very probable that many cases of reflex or vasomotor angina are termed such because of their recovery, which is extremely improbable in true angina. But may not the process in some instances associated with heightened arterial pressure be identical with that which we recognize in advanced arteriosclerosis, and the patient recover as a result of the therapeutic measures which are directed toward lowering the arterial tension? Clinicians generally recognize the curability of the so-called erethistic stage of arteriosclerosis. Is it not equally reasonable to believe that anginal symptoms which disappear after treatment may have an origin identical with that of true angina? The method of production of reflex vasomotor phenomena through the sympathetic nervous system has not yet gained satisfactory experimental demonstration, but the distribution of pain and tenderness has a more tangible anatomical explanation. The distribution area of pain from true angina may be very large and very remote from the cardiac region. The more common regions of referred pain in true angina are the lower cervical and upper dorsal segment, but the pain may be referred to the epigastrium and even to the area supplied by the hypogastric plexus. We are quite sure of the reflex relation between disturbances in rate and rhythm of the heart and stimuli which originate in these remote organs. The vasomotor processes are very difficult to demonstrate experimentally, but it is not a far-fetched inference to ascribe to reflex vasomotor angina from these remote organs the same physiological process which occurs in true angina.

Huchard cites experiments by Moul, who exposed the heart of a curarized animal and employed artificial respiration. From manometric tracings of the pulmonary artery, it was found that irritation of the gastric or intestinal mucosa and bile tract and kidney caused an increased pressure in the pulmonary artery. The interpretation of these experiments was the existence of a reflex vasomotor arc through the cervical cord and grand sympathetic to the superior thoracic ganglia and cardiopulmonary plexus.

This is also the clinical interpretation of many instances described by French physicians, which are described as the pulmonary form, in which dyspnœa is severe, and accompanied by moderate dilatation of the right ventricle, gallop rhythm over the right ventricle, and accentuation of the pulmonic second sound. In these reflex anginas there is no relation between the severity of the lesion and the reflex phenomena. This must be true if the reflex origin of these symptoms from the abdominal organs really exists, because there is no relation between the cardiovascular signs above described and the grave diseases of the stomach, intestines, liver, and kidney. This form of cardiac pain with gallop rhythm over the right ventricle is described in constipation, meteorism, intestinal parasites, dyspepsia, catarrhal jaundice and gall-stones.

It is quite possible that some of the cases of cramp in swimmers are due to vasomotor angina. Bathing in cold water causes cyanosis of the whole body surface, precordial pain, dyspnœa, and tachycardia in some persons. There is a much clearer relation between stomach disturbance and cardiac distress than exists between symptoms from other abdominal viscera and the heart.

Diagnosis.—The distinction between angina vasomotoria and angina due to disease of the coronary arteries may be made by eliciting objective signs of disease of the aorta, myocardium, heart valves, or the arteries. The true angina is characterized by the pain being referred more to the substernal than the precordial region, the pain is accompanied by a sense of constriction, whereas the angina vasomotoria gives a sensation of fulness and pressure in the cardiac region. In true angina there is a direct dependence between exercise and the attacks. The vasomotor-angina patient may be capable of severe physical exercise in the long interims between the attacks. The treatment of angina nervosa or angina vasomotoria will depend on the etiological factors which may be elicited, such as constipation, errors in diet, indiscretion in eating and drinking, or excessive use of tobacco and coffee. The whole manner of life must be investigated. We must learn not only what the patient consumes, but the domestic relations; the manner in which time is given to work and pleasure may have a direct causal relation of the symptoms. Particularly must signs of the early stages of arterial sclerosis be sought for, because much can be done toward the alleviation of symptoms in such cases and the progress of a grave disease may be arrested. The occurrence of angina like attacks with diffuse dilatation of the aorta should be remembered.

The pseudo-angina of hysteria presents a very different picture from the vasomotor angina and true angina. The angina of hysteria is merely an incident in this symptom complex. There are other stigmata present, such as anesthesia of the glottis, narrowing of the visual fields, stocking anesthesia, ovarian hyperesthesia, and other sensory disturbances. Huchard emphasizes the existence of tenderness of the intercostal spaces along the path of the phrenic nerves, and also the presence of a small area of superficial tenderness which is located by the intersecton of two imaginary lines, one an extension of the line of the tenth rib and the other a continuation of the parasternal line. This point is a little above and external to the umbilicus, and is known as the "bouton de Musey." It was first described by Guneau de Musey as a sign of referred pain to the abdominal region from diseases of the lungs and pleuræ and from neuralgia of the phrenic nerve.

The hysterical patient has repeated attacks in a day, as many as 200 having been recorded. Instead of remaining quiet, nailed to the spot and afraid to breathe, the hysterical patient struggles for air, implores aid by vigorous clamoring, makes vigorous efforts to belch gas, has hiccough or yawns, and gapes to get a satisfactory breath. The last symptom is a common sign in vagus neurosis from any source.

In hysterical angina, precordial pain is but one of the many signs present, whereas in true angina and angina vasomotoria thoracic pain dominates the clinical picture. Pain over the precordial region to the left of the sternum and in the left interscapular space is a very common symptom in neurasthenia and occurs in persons not of a neurotic type, as a sign of physical and nervous exhaustion. Under such conditions, however, the pain does not sustain any fixed relation to physical exercise, and movements are not impeded by its presence. Nor are there any accompanying signs of vasomotor disturbances.

RELATION OF NEUROSES TO CARDIOVASCULAR DISEASES.

With the progress of physiological knowledge, functional diseases grow smaller in number, and it is very probable in future years there will be an assignable physiological cause for some of the cardiovascular symptoms we now class under the head of neuroses or functional diseases. But there are many instances of disturbance of function, change in structure, and finally death of the heart due to purely psychical causes. It is generally conceded that arteriocardiac diseases are found with much greater frequency among persons who in early life are neurasthenic and have many signs of vasomotor disturbances. These patients commonly show a wide and tortuous temporal artery. The difficult thing to know in this relation is, if some congenital or vascular defect may not lie at the bottom of the neurasthenia. It seems very reasonable to believe that oft-repeated attacks of tachycardia and arhythmia from gastro-intestinal origin may ultimately cause disease of the myocardium and the coronary circulation.

Anatomical diseases of the heart have long been regarded as atrophic complications of tabes dorsalis. Numerous cases of death from essential paroxysmal tachycardia are reported, but there is considerable doubt as to this affection being a pure neurosis. There is great probability that congenital hypoplasia and myocardial lesions are the sources of this clinical syndrome. We may in this country take a too mechanical view of heart death and ascribe to myocardial exhaustion results which are due to purely nervous influence. The latter conception of cardiac diseases is found much more frequently among French clinicians.

If cardiovascular diseases do result from nervous influence it is apparent that the physician who learns the mental and nervous habits of his patient is in a position to render great prophylactic service. In cases of reflex neuroses the physician should endeavor to learn how much the physical experiences are responsible for the symptoms, and the point from which the original excitation is released. If this latter point can be learned and some procedure instituted which will serve to convince the patient that the cardiac symptoms are purely reflex and not due to grave disease of the heart, much will be accomplished toward a cure of the affliction. We may not understand the exact psychological processes which cause the symptoms, but good judgment on the part of the physician may often direct a mode of living that will enable a patient to escape oft-repeated symptoms which in time may lead to organic disease.

Stokes in discussing the obscurity of the nature of angina pectoris quotes the following from Latham's lectures: "Think what symptoms are. They are not signs of the disease, but they are direct emanations from it; not things in themselves nugatory, but eminently real. They are natural sensations unduly exalted, or unduly depressed, or variously changed or perverted. They are natural functions, hurt, hindered, or abolished. So that a man may often, with strictest propriety, be said to be ill of his symptoms rather than to be ill of his disease, and, what is more, to die of his symptoms than to die of his disease."

Grouping of Cases.—There have been attempts to characterize the cardiovascular neuroses from various causes, but with poor results. In all

cardiac neuroses there is such a mingling of reflexes from the brain cortex and other organs, the stomach, intestines, or generative organs, that it is difficult to know how much significance each source may have. There is just as abundant clinical evidence of nervous cardiac disturbances of all kinds from the brain as from the peripheral nerve supply.

Extrasystole, genuine arhythmia, bradycardia, tachycardia, hyperdiastole, and eventually dilatation and hypertrophy may all result from purely psychical disturbances. It must not be forgotten that all impulses to the heart from the brain cortex find their way through the bulbar centres and are just as much reflex in character as impulses from the abdominal viscera. It is very improbable that cardiac neuroses from any source are unmixed with reflexes from the cerebral cortex, and the more experience one has in following these cases the more this relation becomes apparent. Emotions of fear from dreading an attack, worry over the obscurity of the underlying cause, or a painful sense of guilt, may be factors which will modify results of any reflex stimuli to the heart. There is no one symptom which can be independently linked to stimuli from certain organs. In one patient suffering from cardiac neurosis of gastro-intestinal origin the writer has seen genuine arhythmia, extrasystole, tachycardia, bradycardia, and vagus pulse with hyperdiastole, and all of these various symptoms have been suddenly relieved at one time or another by the eructation of a large amount of gas from the stomach. These attacks gradually grew more frequent during seven years until a method of arresting the tachycardia in its onset was discovered. This gave the patient renewed confidence, and with the exception of very slight attacks at long intervals he was relieved of his cardiac symptoms. The digestive disturbances during all this period remained the same and continued after the cardiac signs practically ceased. So it seems quite justifiable to assume that the cerebral impulses contributed more than the gastric disturbance to producing the heart symptoms. But prior to the renewal of confidence on a justifiable basis it was impossible to recognize the proportion of the psychical factor in the whole trouble.

The attempt to describe the heart disturbances from masturbation as a characteristic clinical syndrome is not justifiable, for here there is the same difficulty of differentiating between psychical effects and reflex disturbances from the sexual organs. The nervous control and direction of the heart is the result of the interaction of excitory and inhibitory reflex influences, and who can estimate the sources of these varying influences during a short period of observation?

The attempt to make a rigid classification of the cardiovascular disturbances in neurasthenia seems quite unjustifiable and unsatisfactory. One author attempts to differentiate between the pulse in the stage of "excitement" and "the latter stage of exhaustion" of neurasthenia, and this too is undertaken with nothing but sphygmographic tracings as a basis. The distribution of the blood in the body is dependent on reflex centres whose equilibrium is in a notoriously wavering state in neurasthenia. It seems a slender basis for clinical grouping of so complex a psychosis as neurasthenia.

Physical Signs.—Physical signs over the region of the heart itself are very misleading in cardiac neuroses. One must always look farther than the heart to prove an anatomical lesion. The evidences of impaired circulation in the lungs, the liver, kidneys, extremities, and central nervous system have the determinating import from a diagnostic standpoint. Murmurs, precordial friction, modifications in the diastolic impulse (gallop rhythm) and all the varieties of arhythmia, bradycardia, tachycardia, and pain may occur in some form of a cardiac neurosis. In prolonged tachycardia, such as the essential paroxysmal type, a genuine passive dilatation occurs. The dilatation is more than a mere active dilatation which is compensatory in character, for it is associated with dyspnœa, pulmonary stasis, cyanosis, and œdema, and yet the heart recovers its normal size so promptly and all its circulatory functions are restored within such a short time that we are compelled to believe a genuine passive dilatation of the heart may exist without a lesion in the myocardium, because such a sudden transition from insufficiency to perfect compensation could not occur under any other than pure nervous conditions. Dilatation and hypertrophy may result from prolonged harmful effects of the emotions. So may hypertrophy result from purely nervous influences, as described in Vaquez's cases of brachial stump neuromata accompanied by tachycardia. Murmurs associated with the heart functions which are not caused by pathological lesions in the valves or myocardium are very obscure in their origin.

The method of production of the *cardiopulmonary* murmur is as follows: A piece of aërated lung lies between the contracting heart and the anterior thoracic wall. The lung is compressed between the heart and the thoracic wall so that the air expelled from a tongue of lung thus compressed has a velocity sufficient to produce a murmur. The character of the murmur, its pitch, intensity, and quality will be modified by the force and rate of compression and the contents of the air spaces. If there should be a considerable amount of fluid in the air spaces, the murmur will have a bubbling or even a splashing character. The rasping character of these murmurs over the site of the conus arteriosus of the right ventricle, where precordial movement in an anterior direction is great, often simulates the friction of pericarditis. These murmurs may be so loud as to be heard at a distance from the chest wall. The most striking instance and also the most convincing proof of the manner of production of the cardiopulmonary murmur seen by the writer occurred in a case of bilateral thoracic empyema. Both lungs were displaced toward the median line so that the precordial area was tympanitic and the cardiac cycle was accompanied by a loud, rasping friction and bubbling. All the sounds over the tympanitic precordial area had a ringing tympanitic quality which sounded as though they occurred in the presence of fluid and air. The sounds were so loud they could be heard by the unaided ear six inches from the chest wall. The autopsy revealed only the bilateral empyema, with both lungs crowded in front of the heart. There was not the slightest evidence of disease of the heart or pericardium, although the signs led the writer to make a diagnosis of pyopneumopericardium due to some gas-forming bacterium.

The occurrence of cardiopulmonary murmurs offers a very plausible explanation for many murmurs heard over the heart during excitation of its action. Potain's explanation of the systolic cardiopulmonary murmur is quite satisfactory, but the diastolic cardiopulmonary murmur does not admit of so ready an explanation. Potain believed that the diastolic murmur was due to rapid reëntrance of air into the tongue of lung which was compressed during the systole of the ventricle. An explanation of the endocardial murmur not caused by relative insufficiency of the valves is lacking at present.

Modifications in rate and rhythm from nervous influences are very familiar experiences. We know that nervous phenomena may be responsible for chronotropic, dromotropic, bathmotropic, and inotropic influences. This being true, it is not difficult to understand how gallop rhythm, diastolic impulses, and heart-block may be the result of purely nervous influences. With all these possibilities in view, one is reminded of the great caution which must be employed in differentiating between functional and anatomical disease of the heart. There are no fixed rules for differentiating the several signs caused by functional disturbances from those due to anatomical lesions. It is only by considering the general circulatory condition of all the organs of the body that a diagnosis can be made. Besides these adventitious phenomena we not uncommonly find a modification of the heart sounds to which we are accustomed to ascribe considerable diagnostic import in endocarditis. The systolic sound in tachycardia may become loud and high-pitched if the tachycardia is accompanied by dilatation. This is a common occurrence in the essential paroxysmal tachycardia, but is not seen in the reflex tachycardia from gastro-intestinal disturbances. A loud systolic sound over the apex and a loud diastolic sound over the conus arteriosus are frequent in paroxysmal tachycardia with dilatation. Proximity of the heart to the chest wall will contribute to the intensity of both the systolic apex sound and the second sound over the conus arteriosus. The shortened and incomplete systole of compensatory dilatation is also a probable factor in accentuation of the systolic sound at the apex.

To differentiate between functional and anatomical diseases of the heart often requires repeated observations over a long period of time with a patient under varying physical conditions and also in some instances with a change of social relations. Domestic infelicity and other disappointments in life are occasionally causes of disturbances of rate and rhythm. Stokes (1853) says: "The facility of making a correct diagnosis between functional and organic diseases is not so great as modern writers led us to believe. And we more often arrive at a just conclusion by instinctive skill, the result of experience, and judgment, than by communicable rules of diagnosis."

Palpitation.—This is a term used by patients to express the fact that their heart's activity lies within their own consciousness. In clinical experience it is not synonymous with tachycardia. Many neurotic patients acquire a consciousness of the heart's action when there is nothing abnormal to be detected. These patients seem to acquire consciousness of the normal heart's action just as some patients acquire consciousness of

the normal digestive processes in the stomach and intestines. Paroxysmal tachycardia without dilatation of the heart may give the patient no sense of palpitation. A patient with a heart rate of 250 will not complain of the least sense of palpitation. Fever patients do not complain of palpitation. Another patient with a heart rate of 50 complains of palpitation as the most disturbing symptom. In tachycardia associated with the sense of palpitation there is an active dilatation of the heart. The sensation of palpitation is closely linked to the hyperdiastole of vagus irritation and is quite independent of the heart rate and force of the apex beat.

PAROXYSMAL TACHYCARDIA.

Essential paroxysmal tachycardia is a term credited to Bouveret,[1] who collected the cases published to 1889 and employed this term to describe a train of symptoms which was unassociated with known anatomical lesions or reflex mechanism. Although cardiovascular pathology and physiology have made great progress in the past seventeen years, the term essential paroxysmal tachycardia remains a suitable one for the grouping of these clinical cases, for which there exists no satisfactory physiological or pathological solution. By common consent among medical writers, the term tachycardia may be applied to a heart rate above 120, but there is a wide gap between the tachycardia of infectious diseases or exophthalmic goitre and the heart rate of paroxysmal tachycardia. In the latter a heart rate of 240 is common and a rate of 300 to the minute has been observed. When dilatation and asystole occur in this affection, they are the direct result of the tachycardia, whereas in the other affections the tachycardia is secondary to exhaustion from toxic effects as well as the tachycardia. In essential tachycardia the heart rate always attains a rate of 200 or more within a short time following the beginning of the attack, and with few exceptions the high rate is attained directly the attack begins. Tachycardia is the one symptom which dominates the whole clinical picture and sustains no secondary significance to any other pathological sign. The causes underlying the tachycardia (whatever they may be) are primary and all other signs are results.

In his original classification Bouveret tried to exclude all those paroxysmal tachycardias which were associated with bulbar diseases, affections of the vagi or myocardium, and all those due to reflex stimuli from other viscera and intoxications of all kinds. He did not, however, make a satisfactory differentiation in his cases. This attempt at classification has not been followed by subsequent writers. All of the associated affections which Bouveret attempted to exclude have been included in the collected cases of later students of the subject. A. Hoffmann[2] collected 126 cases with 16 autopsies: 11 cases showed myocarditis and 2 other cases were described only as dilated hearts without further study of the myocardium. As in every other clinical field in which the pathology is not clear. writers differ in the acceptance and rejection of cases for various reasons.

[1] *Revue de médecine*, 1889, ix, 753.
[2] *Die Paroxysmale Tachycardie* (Wiesbaden, 1900).

This we must expect when we are dealing with a symptom which has no known physiological or anatomical cause. Hoffmann makes the following etiological classification: mental excitement and fright, 23; head injuries, 3; organic brain diseases, 2; exhausting diseases and toxic causes, 19; disturbances of the abdominal organs, 23; heart affections, 24; physical exertion, 21; and in 21 cases there was no assignable cause. Bradycardia as we see it clinically can be reproduced experimentally by a number of attacks at different points in the neuromyocardial system, but polysystole such as we see in paroxysmal tachycardia cannot be produced through the nervous system. The only method of approximating it experimentally is by an accumulative series of extrasystoles which result from irritation of the myocardium.

Apparently, we have to deal with the combined results of positive chronotropic and positive bathmotropic influences and from clinical experience, we must believe the origin of paroxysmal tachycardia is due to some combination of these two influences somewhere in the nerve supply of the heart. The heart stimulus is constant, but the rhythmic cardiac cycle is due to the interaction of inhibition and excitation, which gives the resulting spaces of the several phases of a cardiac cycle. We can compare the flow of energy in the heart's stimulus to a filter under pressure. Although the pressure is constant the flow is interrupted. If the wall of the filter be injured, inhibitory influence is suspended and we have a continuous stream instead of an interrupted flow. This seems to be what really occurs in paroxysmal tachycardia; the inhibitory influence is suspended and, instead of the rhythmic spacing of phases which occurs in more moderate polysystole, we have the phenomena of embryocardia with abolition of the postsystolic refractory period. There is not only a positive chronotropic influence, but also a positive bathmotropic influence which increases the irritability of the heart.

Symptoms.—The first intimation of an attack is the "flop" or "tripping" of the heart. This manifests itself by a throb and sense of oppression over the precordial area and a slight sense of fulness in the vessels of the neck. This is caused by extrasystole which usually precedes the tachycardia. Sometimes the first sensation is that of fainting due to cerebral anemia, as the extrasystole is very feeble and is succeeded by a long compensatory pause. Several extrasystoles commonly follow and then suddenly the furious storm of tachycardia appears. In one patient, whose pulse was being felt when an attack began, there were three or four extrasystoles clearly palpable before the attack commenced. It is doubtful if extrasystole always ushers in the attack. Patients describe some of the attacks as beginning instantly without the least sense of a "heart-flop" preceding the tachycardia.

The termination of an attack is as prompt as the onset. The rapid rate ceases instantly and is followed by a long pause; then a full strong impulse is felt over the heart, accompanied by a full pulse wave at the wrist. There may be several irregular heart beats and then the normal rhythm and rate are reëstablished, accompanied by a sense of "glow over the whole body." The "flop" and several irregular beats are more constant in the conclusion of the attacks than in the beginning. The relation

between paroxysmal tachycardia and Stokes-Adams syndrome has been remarked by several observers. The writer observed the transition from tachycardia to bradycardia in a patient who had been under observation for eight years and who was seen in about twelve paroxysms of tachycardia. The patient has had only one attack of bradycardia. The onset of this attack was with the usual tachycardia of about 220 beats to the minute. After this had lasted about an hour there was a sudden change from tachycardia to bradycardia with arhythmia. There never had been any arhythmia with the tachycardia. The pulse, which to that juncture was rhythmic at 200 or more, suddenly slowed to from 12 to 16 beats in a minute and was very arhythmic. During the bradycardia the external jugular veins and the bulbus venosus were markedly distended. There was no distension of the external jugular veins during tachycardia. The veins pulsated very rapidly, but unfortunately at that time observations did not go beyond this and the proportionate rate of pulsation between the veins and the artery was not observed. That the veins were distended and pulsated rapidly when the radial pulse was slow, full, and irregular was noted at the time. The change of feeling in the patient was very marked with the advent of the bradycardia with heart-block. The patient had learned to endure the tachycardia, but with the slow pulse there was a sense of anxiety and depression, and every systole was accompanied by a strong throb over the heart area. The bradycardia lasted about half an hour, when suddenly, after the eructation of a large amount of gas from the stomach, the heart resumed its normal rhythm and rate of 76.

Here was an example of a cause producing a series of extrasystoles in the guise of tachycardia which (by some change in the interaction of excitation and inhibition) suddenly transformed the picture of positive chronotropic and positive bathmotropic influences to that of negative chronotropic with negative dromotropic influences.

It is doubtful if all cases of paroxysmal tachycardia are due to a series of extrasystoles. If the classification of paroxysmal tachycardias could be made on this basis we could make one step toward a satisfactory grouping of cases. Such a classification would be more satisfactory than the attempt to classify them on an etiological basis, when we have no physiological understanding of the process.

Some patients seem to endure their tachycardia with little discomfort and walk about attending to their business with a heart rate of 200 or more. The sense of palpitation is not distressing to some patients; there is then no hyperdiastole. One patient was seized with an attack on a holiday excursion while exploring a ravine a hundred feet deep with densely wooded banks. She climbed out of the ravine and walked from the top of the bank over a freshly ploughed field with a sharp upgrade to a farmhouse, a quarter of a mile distant, and experienced no dyspnœa during the effort beyond what she would have experienced under normal conditions.

The patient as a rule prefers the horizontal position. There is a sense of constriction in the epigastrium and some precordial anxiety. There is a partial aphonia. The face may be pale, or livid and cyanotic; the jugular veins may or may not be distended. These signs will vary with

the vasomotor influences and whether asystole with dilatation has occurred or not. The pupils have been observed to be dilated, contracted, and unequal in different cases, and to vary during a single attack. Profuse sweating is an unusual symptom, although it sometimes occurs. The duration of attacks varies from a few hours to six or eight weeks. The presence of other symptoms will depend upon the endurance of the myocardium. There may be a murmur with the systolic sound or a postsystolic murmur. It is more common to find the heart sounds clearly defined even in instances occurring with valvular disease. The murmurs which are present during the usual rate become inaudible with the advent of a tachycardia. Signs of stasis do not appear until the attack has lasted several days and the attack may last many days without any such signs appearing.

When signs of *stasis* do appear, there may be dilated veins in the neck, cyanosis, pulmonary œdema with hemoptysis, swollen liver, and albuminous and bloody urine, œdema of the extremities, and mental confusion. With cardiac dilatation and asystole there is a danger of thrombi forming in the heart chambers and all the possible results from emboli may occur. The existence of such signs, however, does not justify an absolutely bad prognosis, as we learn from Pribram's case of a young woman in whom the pulse rate was at first 220 and then gradually rose to 300. On the fifth day signs of stasis developed. The first sound was replaced by a murmur. Pulmonary stasis, œdema, cyanosis, and dilated heart all pointed to impending death. The patient gave a start and the heart resumed its normal rhythm and rate of 76, and a prompt recovery followed. The pulse in all the patients who have come under personal observation was of small volume, very low pressure and monocrotic, although dicrotism is described in some instances and in other cases the pulse is described as having a maximum pressure little below the normal and of the celer type. Tolerance of these attacks varies in the individual, and from the autopsy reports we should judge that the resistance of the myocardium is the determining factor.

Marked vasomotor disturbance seems to accompany the tachycardias with grave signs of myocardial incompetency. Pel[1] described one instance of tachycardia during a tabetic crisis with a heart rate of 240 and maximum arterial pressure of 60 mm. Hg., and at this time the pulse was hyperdicrotic. He expresses the opinion that tachycardia which does not cause cardiac dilatation, dyspnœa, cyanosis, or any signs of stasis, is due to the effects of vasodilator influences.

In the light of modern research on cardiac innervation, it seems more reasonable to believe that such cases are due to extrasystole and offer a favorable prognosis compared to the tachycardia which is myocardial in origin. Clinical evidence tends to show that paroxysmal tachycardia may result from diseases of the medulla or reflexly through the medulla, from affections of the vagi and from the myocardial diseases. Whether any of the cases are due (as Pel believes) to vasomotor relaxation in the splanchnic vessels or not is difficult to determine, because it is not settled

[1] *Gefässkrisen*, Leipsic, 1905, p. 51.

in any given case if the change of position arrested the tachycardia by blood gravitating out of the splanchnic vessels or if the same procedure did not increase the tone of the vagus inhibitory centre in the medulla and thus slow the runaway heart. Spengler's patient had a heart rate of 80 when lying down and 250 when standing. This is termed orthostatic tachycardia. J. Lardin[1] discovered he could stop his own tachycardia by leaning forward with his arms hanging down. Some persons subject to paroxysmal tachycardia can stop the attacks by standing vertically in a corner with the head down. In others firm bandaging of the abdomen stops the attacks, but it is not absolutely proved that emptying the splanchnic veins gives the relief. Relief from this procedure may come through stimulation of the medulla.

One patient with paroxysmal tachycardia was fifty-six years of age and suffered from myocardial disease which dated from an attack of lobar pneumonia six years before. She had also phlebitis of both femoral veins after the crisis of the pneumonia. The attacks of tachycardia were rare, in all not more than seven in six years. The heart rate did not exceed 180 and began rather gradually, reaching the maximum rate in about half an hour's time. The rate of 180 persisted as a rule for about ten hours and then gradually subsided to about 140, when the normal rate of 80 was suddenly resumed. There was no cyanosis, dyspnœa, stasis, or polyuria during the attacks. The pulse was not extremely small, but exhibited about the volume to be expected in such a short diastole. There were no evidences of vasomotor disturbances in the extremities or in the splanchnic area. There were no disturbances in the stomach or intestines associated with the attacks, nor eructations of gas at the conclusion of the tachycardia. It is conceivable in such a case of myocarditis that a series of extrasystolic impulses liberated at Gaskell's bridge may have been the cause. No clear evidence of ventricular extrasystole could be demonstrated. There was no cardiac dilatation during the attack, and the patient walked about the room with no more difficulty apparently than when the heart rate was 80.

Neusser[2] described one case of intermittent tachycardia in which the attacks were accompanied by meteorism which he interpreted as originating through the vagus affection due to pressure from tuberculous mediastinal glands. The heart rate during the attacks was only 160, but experience shows that tachycardia from disease of the vagus nerve need not be constant, as is assumed by Martius; spasmodic asthma and pulmonary emphysema may be due to the same cause. For the bulbar origin of some cases of tachycardia the following evidence is offered: polyuria, modifications of the pupil, herpes labialis, vomiting, and vasomotor disturbances in the splanchnic distribution.

Treatment.—The treatment of any given attack suggests first to attempt to influence the heart rate by the position of the body. The very simplest device is to place the patient with the head down and legs elevated, which may be done (where advisable) by laying the patient on a board or hospital litter. Tight bandaging of the abdomen may be

[1] *L'union médicale*, August 21, 1875.
[2] *Ausgewöhlte Kapitel der klinischen Symptomatologie und Diagnostik*, Heft 1, p. 38.

employed when the pulse volume is small and there is no dyspnœa, cyanosis, or signs of dilated heart.

An ice-pack or ethyl chloride spray over the nape of the neck may be used with the hope of securing vagus inhibition reflexly from the medulla. Compression of the vagus trunk in the neck at the level of the angle of the thyroid cartilage has been efficient in arresting the attack in several cases. If pressure over the vagus is not successful, galvanization of the vagus may be tried, which according to Huchard should be done in the following manner: A current of from 2 to 4 m. should be used. The positive pole is applied at the nape of the neck and the negative pole midway on a line connecting the mastoid process with the angle of the thyroid cartilage. Each vagus should be treated two or three times daily and for four or five minutes at each time.

Adrenalin, quinin, ergot, and nitrite of amyl have all been employed as the vasomotor tone of the arteries suggested, but there is little to be hoped for in the employment of any drug.

Protection against the recurring attacks may be favored by leading a life both morally and physically hygienic. Abstinence from tea, coffee, alcohol, and tobacco should be strictly observed. Any dyspepsia of gastric or intestinal origin should be carefully investigated. Many attacks of paroxysmal tachycardia have their origin in gastro-intestinal disturbances.

STOKES–ADAMS SYNDROME.

The Stokes-Adams syndrome is a group of symptoms which may involve crises in the vascular supply of the brain and medulla and myocardium, and negative chronotropic and negative dromotropic influences originating somewhere in the tract of the vagi, also negative dromotropic influences due to disease at the atrioventricular bridge, thus implicating that portion of the myocardium which passes from auricle to ventricle through the atrioventricular sulcus. Or there may be negative bathmotropic and chronotropic stimuli manifested at the auricles where the constant stimulus is believed to originate. The term "Stokes-Adams" is applied to certain symptoms and not to a definite pathological process. It is not synonymous with heart-block. The causes which give rise to the symptoms may produce their manifestations through irritation of the medulla, upper cervical cord, and vagus trunk, or there may be in addition to the purely nervous influences some lesion in the myocardium which contributes to the slow heart rate and arhythmia commonly present. But bradycardia is not responsible for the cerebral symptoms which accompany the paroxysms. The symptoms vary with the disease of which they may happen to be a manifestation. The clinical picture of pressure on the medulla or upper cervical cord would differ widely from that of sclerosis of the brain arterial supply with chronic interstitial nephritis and sclerosis of the coronary arteries with secondary disease of the myocardium.

The symptoms are both cerebral and cardiac in origin, although bradycardia and arhythmia are the most striking features in many cases. Nervous influences may cause a bradycardia or rather slow pulse in

several ways. There may be negative chronotropic or negative bathmotropic influences applied to the supposed seat of origin of cardiac rhythm, namely, at the junction of the veins with the auricles, or on account of negative dromotropic influences at the atrioventricular junction heart-block may result, and although the auricle continues a normal or rapid rate, the systolic wave is blocked at the atrioventricular junction and the ventricle does not share in the systole. This procedure can be distinctly seen with the fluoroscope. The contractions of the right auricle can be clearly seen and during the block the ventricle is seen to gradually enlarge, and with a complete heart cycle the systole of the ventricle can be clearly seen to succeed the systole of the auricle. So we may have a bradycardia from purely nervous influences which involves auricles and ventricles, or a bradycardia which involves the ventricle only. In both conditions of course there is a slow pulse. The real problem, so far as the heart is concerned, is to determine whether we are dealing with a genuine bradycardia which involves both auricles and ventricles, or heart-block, in which the rhythm of the auricles is maintained, but the ventricle fails to follow. The other problem to determine is where the nervous stimuli arise, in the brain, medulla, cervical cord or vagi, and whether these stimuli arise from disturbances in the vascular supply to these parts or from pressure or intrinsic disease of these structures.

By far the most common association of the Stokes-Adams syndrome is with arterial sclerosis, and in this affection the three organs which suffer mostly from secondary effects are the heart, brain, and kidney. Vascular crises in different parts of the arterial supply are common in this disease. Besides the results of vascular crisis in the arterial supply to the brain there may be many symptoms constantly present. Sclerosis of the coronary arteries commonly results in secondary diseases of the myocardium, which may cause a genuine bradycardia and also heart-block. We have the pathological conditions for bradycardia and heart-block constantly present, and also the necessary conditions in the arterial supply to the brain which produce paroxysmal attacks of bradycardia and heart-block. The other symptoms from the brain are very commonly seen in persons with sclerosis of the cerebral arteries. His[1] recognized the significance of these symptoms in relation to the myogenic theory of the cardiac rhythm (as conceived by Gaskell) and also the rôle of "Gaskell's bridge" in the embryology and physiology of the heart as described by Stanley Kent.[2]

Symptoms.—The patients are usually past middle life and present signs of arterial sclerosis. Bradycardia and arhythmia are constantly present. The heart rate is commonly 40 or thereabouts, but during the paroxysms the rate becomes slower. In one fatal case described by Huchard the rate was as low as 2 to the minute. The pulse may be very irregular. There is not a constant relation between the cerebral symptoms and degree of bradycardia and there is no reason to regard the brain symptoms as secondary to the bradycardia. A heart rate of 30 may

[1] *Deutsch. Arch. f. klin. Med.*, vol. lxiv.
[2] *Journal of Physiology*, vol. xiv, p. 229.

accompany an apoplectic or epileptic seizure, and the same rate with perfect rhythm has been seen in a neurasthenic man who complained chiefly of symptoms due to dyspepsia. Under paroxysmal tachycardia one instance of sudden transition from paroxysmal tachycardia to paroxysmal bradycardia and arhythmia with a heart-rate of only 16 to the minute has been noted. There were all the signs of heart-block one sees in the Stokes-Adams syndrome. Yet there was not the slightest suggestion of any cerebral symptoms. There is very strong evidence that the bradycardia of the paroxysms has its origin in negative chronotropic impulses from the cardiac nerve supply either in the medulla or in its path from the medulla to the heart.

The *cerebral* signs are due to crises in the vascular supply to the brain and medulla. These may vary greatly in character with the severity of the attack and the parts of the encephalon chiefly implicated. The attack may be merely syncopal, epileptic, or apoplectic in character, with stertorous breathing or even Cheyne-Stokes respiration, but at autopsy no pathological signs are found in the brain tissue which can be associated with the paroxysm. This is quite conceivable if we think of the vascular spasm and its results as seen in the retina, extremities, and intestines. Both irritation and anemia of the medulla cause slowing of the pulse. Halberton's case, one of the earliest of this kind described and referred to by all writers on the subject, was that of a man who developed the symptoms three years after a fall from his horse in which he struck on his head. The autopsy revealed narrowing and deformity of the foramen magnum, and thickening of the dura mater which was sufficient to compress the cervical cord and medulla. Other cases of Stokes-Adams syndrome have been observed which have come to autopsy and skilled pathologists were unable to demonstrate any lesion in the medulla or in the cardiovascular system.

The whole symptom complex may arise from irritation of the *vagus* trunk. Probably the best evidence is to be found in Tanhoffer's[1] description of his experience with a pupil who was making some experiments on his own vagi for his professor's benefit. This student compressed with his left index finger and left thumb respectively his right and left vagi. Tanhoffer observed, while making sphygmographic tracings of the pulse, that his pupil did not respond to a question. On looking at his face, Tanhoffer observed his eyes had a glassy stare, and the left arm was rigidly contracted, with the finger and thumb pressing at the throat. The student had lost consciousness. Tanhoffer pulled the hand away from his throat and observed the pulse had ceased, the sphygmogram showing no tracing of the pulse for 67 seconds; then the pulse steadily rose in frequency. The student was unconscious for several minutes, and when consciousness returned he was dizzy and nauseated.

The physical signs over the heart, besides the bradycardia and arhythmia, vary with the manner of heart-block or bradycardia. In instances of heart-block one may count the pulsations in the external jugular vein, as the veins of the neck under such conditions are greatly dilated.

[1] *Centralblatt f. med. Wissenschaft*, 1875, p. 403.

Under such conditions there can be seen two or more distinct pulsations in the veins for every pulsation in the artery. When the tricuspid valve is sound the venous pulses are due to the contraction of the auricle and can be seen to precede the carotid pulse in a complete cardiac cycle, and when the block at the auriculoventricular bridge occurs a pulse is visible in the jugular vein which marks the systole of the auricle.

The ventricles manifest some signs during the blocked systole. Although no pulsation occurs, one may hear a very faint sound over the ventricles. This is probably due to the closure of the atrioventricular valves which marks the termination of the auricular systole. At other cycles there may be an impulse over the ventricle due to an extrasystole which originates from the bridge and is not sufficient to produce a pulse, or, as Huchard suggests, such pulsations are due to distension of the ventricles from the auricular wave. This point can be determined only by an analysis of the comparative tracings of the venous and arterial pulses and cardiac impulses.

In one patient with a typical Stokes-Adams syndrome a marked improvement followed vigorous antisyphilitic therapy with both mercurials and iodide of potash. After this improvement, the heart rate remained at 60 to 70 per minute unless the patient exercised; then the heart rate became slow as before. The fainting, clonic convulsions, recovery from heart-block under antisyphilitic treatment, and subsequent slowing of the heart rate with exercise, all lure us to the ready conclusion that the heart-block was due to syphilitic disease of the bundle of His. But there were other features which serve to throw doubt on this explanation. The patient had sclerosis in all the accessible arterial distributions. During five consecutive months in which heart-block persisted, the patient dared not fall into a deep sleep. Whenever he went soundly to sleep automatic respiration ceased. If he was permitted to lie in this state of apnœa until he awakened spontaneously, he awoke with air hunger which was very distressing. The heart rate was not in any way implicated in this procedure.

During the greater part of the night the nurse awakened him promptly when respiration ceased. This procedure prevented the patient getting any sleep until the early morning hours, when he would finally fall into a light sleep which did not interfere with automatic respiration. After this prolonged siege with heart-block and slumber apnœa which lasted five months, his pulse was observed one morning to have attained a rhythmic and regular rate of 60 per minute. From that time on he could sleep soundly through the night without any respiratory disturbance. The manner of recovery here does not offer any respiratory proof that the slumber apnœa and heart-block were both due to bulbar disease from sclerosis of the basilar arteries, but we know a definite relation exists between slumber apnœa and sclerosis of the cerebral arteries and we know of no causal relation between bradycardia and slumber apnœa. Such a case suggests the need of careful histological studies of the bulbar nuclei in cases of Stokes-Adams syndrome.

Disease of the bundle of His no doubt explains some cases of heart-block, but it is improbable that it will explain all cases any more than

myocardial disease will explain all other changes in rate and rhythm of the heart-beat. There is another significant fact relative to this point, viz., the bulbar origin of the Stokes-Adams syndrome. Some cases have been reported in which the paroxysms of bradycardia and accompanying brain symptoms could be avoided by inverting the body. If measures which increase the blood supply to the brain will stop the paroxysms of Stokes-Adams disease, it seems reasonable to assume that bulbar anemia (in some cases at least) causes the heart-block.

Prognosis.—This is grave in any case of Stokes-Adams disease, though a prognosis for a short duration of life is not invariably justifiable. The course may be chronic but there is always the chance of sudden death. Frequent attacks and prolonged syncope are grave signs. In 1904 the writer, with S. J. Webster, saw a man aged seventy years, who had his first attack of convulsions when sixty-three years of age. Subsequently there were two more attacks. When serving as a soldier it was observed that he had a normal heart rate of 40, which rose to 50 under excitement. His health remained good until the attack seven years ago. He had a much enlarged heart, marked arterial sclerosis, and dilated and pulsating jugular veins. The carotid artery showed 36 pulsations to the minute. The jugular vein showed 72 centrifugal pulses to the minute and these were equidistant; so they were pulses from two distinct cardiac cycles, one of which was blocked and the other transmitted to the ventricle. A few months later Dr. Webster found the precordial area had increased in size, the distress and dyspnœa had increased, and there were three venous pulses for each arterial pulse. In the summer of 1907 the writer found him very much better. The venous pulses had entirely disappeared; the area of cardiac dulness had diminished, and the pulse rate was rhythmic, 76 per minute, and the arterial tension was markedly increased.

Treatment.—Besides the treatment of the underlying cause, such as syphilis, arterial sclerosis, and brain affection, the only specifics for the symptoms are: to put the head low or invert the body to counteract the anemia of the brain, which is supposed to be the cause of the symptoms, and to employ atropine to diminish the inhibitory tone of the vagus termination. Atropine is of service when the bradycardia is not due to heart-block or affections of the myocardium itself. In heart-block, Erlanger[1] has shown that atropine increases the rate of the auricle and not the rate of the ventricle. Dehio has shown the efficacy of atropine in increasing the heart rate when the vagus inhibitory tone is increased and the failure to give relief when bradycardia is due to disease of the myocardium; but his conclusions should not be rigidly adhered to in treatment, because benefit in myocardial cases may be got by diminishing the normal negative dromotropic influence of the vagus nerve or vagus nucleus.

Syphilis must not be forgotten in treating any case of Stokes-Adams syndrome. Syphilitic myocarditis involving the bundle of His has been proved in several cases at autopsy. Syphilitic arteritis of the cerebral arteries may also be a cause. Not only iodide of potash, but mercury in

[1] *Journal of Experimental Medicine*, vol. vii, No. 4, and vol. viii, No. 1.

sufficient doses must be used, for the chronic arteritis of syphilis responds to mercury when it is unaffected by iodide of potash, although the primary infection may have occurred many years before.

DIGESTIVE DISTURBANCES AND THE HEART.

Circulatory disturbances, caused by disorders of digestion, are comparatively frequent. These patients are rarely so ill that they are confined to bed, and relatively few obtain admission to hospital wards. They are too often regarded as hypochondriacs with the imputation that autosuggestion is the source of their trouble. It is very difficult to determine how much the psychic factor shares in their suffering, and how much the patient's fears contribute to the cause of their symptoms. This is not difficult to understand when we consider the character of cerebral reflex cardiac symptoms. The patient who has once suffered a paroxysmal tachycardia is left in constant fear of a recurrence. They become depressed, and this increases the disturbances of digestion, until finally such a patient lives in constant terror. From these very sources, however, there can be much learned about the nature of cardiovascular disturbances and the nature of nervous influences over the cardiac cycle.

Secondary to defects in the digestive processes we may have very great modifications in the distribution of blood. There is a constant equilibrium maintained between the splanchnic vessels and the vessels to the limbs, head, and surface of the body. To appreciate this fact, one need only to watch the pulse of a patient during the operation of gastro-enterostomy and observe how the splanchnic vessels swell with blood and how the radial pulse fades when there is any traction exerted on the omentum and mesentery. With such experiences in mind, it is not difficult to conceive why many patients with gastro-intestinal dyspepsia and ptosis of the stomach and intestines suffer from cold hands and feet and have a radial pulse of small volume with low pressure. Some people become very chilly after each meal and invariably walk from the dining table to the open fire or radiator. Why disturbances of blood pressure, blood distribution, and heart rhythm are not more frequently seen in diseases of the digestive organs seems strange. A conspicuous feature of these symptoms, however, is their association with digestive diseases of mild type, while ulcer and cancer of the stomach, obstruction of the bowels, peritonitis, ascites, and meteorism are never associated with such cardiovascular symptoms. Explanatory of this disparity has been offered the suggestion that "grave diseases depress the reflex centres, whereas the milder affections are associated with exaltation of the reflexes." This is merely a response, not an answer to the question. To liberate these reflex stimuli to the heart and vasomotor centres it seems necessary for the viscus not merely to suffer distension, traction, or pressure, but these forces must be applied at certain points and in certain directions. These points have not been sufficiently investigated from an experimental or clinical standpoint to justify a positive statement.

No doubt the mental status of the patient is often a determining factor in the production of these symptoms. The person who enjoys mental

tranquility maintains an inhibitory tone over his bulbar centres which the neurasthenic and hysterical patients have lost, and, as a consequence, the same impulses from the abdominal viscera meet with different responses in the centres of the medulla or spinal cord. There are symptoms from the heart ascribed to digestive disturbances which are more than mere disturbances in cardiac innervation. These symptoms include not only a vasomotor spasm in the pulmonary arterial branches, but also a passive dilatation of the right ventricle with stasis in the venous system which may lead to œdema of the extremities. This clinical interpretation is found particularly among French writers. A patient is described as having a rapid pulse of small volume with accentuated second pulmonic sound and palpable diastolic impact over the pulmonic area. The right heart is dilated with gallop rhythm confined to the right ventricle; the liver is slightly enlarged and sensitive to slight pressure. In severe cases the patient may have dyspnœa, cyanosis, and œdema. These patients are kept in bed, put on a slender diet, and given mercurials and saline cathartics in moderate doses, and with relief of the splanchnic vessels the cardiac symptoms disappear. Cases of pure gastric disturbance due to hyperchlorhydria have been described with this train of symptoms and appropriate treatment of the gastric disorder was followed with relief of the heart symptoms.

Such signs of myocardial incompetency relieved by the treatment described are not uncommon in any hospital ward, but the interpretation of cause and effect is the reverse of that described. We regard the hepatic and gastro-intestinal symptoms as secondary to the myocardial incompetency and the relief afforded by the treatment as due to lowering the arterial resistance in the splanchnic vessels and the relief to the myocardium from rest in bed. This is a subject which requires further investigation. Traction on the mesenteric attachments apparently causes intermissions in the heart beat as well as an impaired blood supply to the head and extremities. Patients with lax abdominal walls and ptosis of the viscera sometimes experience relief from cardiac intermissions and improve their mental state by applying a good abdominal support. A most unequivocal experiment on distension of the stomach with its results to the cardiac rhythm was performed unwittingly while attempting to learn the relation of an epigastric tumor to the stomach. The patient was given the usual amount of bicarbonate of soda and tartaric acid to inflate the stomach. It was later learned that the palpable epigastric tumor was only a part of a carcinomatous growth which involved the whole stomach and had transformed it into an unyielding, rigid sac. The patient sat on the edge of the bed during the procedure, and directly the second draught was swallowed he showed signs of great distress. He became livid; the jugular veins were enormously distended and pulsated rapidly. The arterial pulse was very slow and arhythmic, although full and of fair pressure when it did occur. There was not sufficient time to determine the rate of the pulse with accuracy, for the whole procedure could not have lasted more than half a minute. The rate, however, was estimated at the time as being less than 20 per minute. With the eructation of gas from the stomach the normal color returned to the face; the jugular veins collapsed

and the heart became rhythmic, with a rate of 80 per minute. Whether this patient had a genuine bradycardia or heart-block is not perfectly clear, although the marked distension of the jugular vein and the slow arhythmic arterial pulse of full volume are evidences of heart-block. The symptoms, so far as the heart was concerned, were identical with those in Stokes-Adams syndrome.

It is common experience to see extrasystole or tachycardia accompany gastric distension, but in the experiment just described an intragastric pressure was reached which is never seen in the natural course of a dyspeptic attack. Under essential paroxysmal tachycardia an instance of transmission from tachycardia to bradycardia with heart-block is described. The change from tachycardia to bradycardia was as sudden as the onset of the tachycardia. A comparison of these two cases suggests that the appearance of tachycardia or bradycardia with heart-block will depend on the degree of intragastric pressure which is developed. Constant bradycardia is not extremely rare as a neurosis of the heart in conjunction with digestive disorders, but the cases which have come under personal observation have not been reflex in character as the two above described. The other cases were true bradycardia without arhythmia, and were due either to some toxic condition which originated from the digestive disturbances or were direct symptoms of the psychosis. The latter seems more probable.

During these attacks of reflex tachycardia from distension of the stomach, the stomach does not protrude in the epigastrium. We know that the dome of the cardiac end of the stomach may stand on a level with the third intercostal space in the nipple line and still cause no protrusion in the epigastrium. Clinical evidence tends to show these reflex impulses to the heart are liberated from the cardiac end of the stomach and œsophagus and not from the pyloric end of the stomach. If direct pressure against the under surface of the diaphragm which displaces the heart were sufficient to liberate a series of ventricular extrasystoles by direct irritation of the atrioventricular bridge, then meteorism, ascites, and large abdominal tumors should commonly be associated with tachycardia. But, as we have seen, severe distension of the stomach is associated with bradycardia and heart-block and not with tachycardia. Reflex tachycardia from gastric disturbances begins and ends with the same suddenness as attacks of essential paroxysmal tachycardia. Unlike these cases, however, the attacks are not so long in duration, rarely more than two hours. The patients are not cyanotic or dyspnœic. The jugular veins are rarely dilated, and there is rarely any dilatation of the heart. The pulse is always extremely small, so small indeed, with a heart rate of 240, that it is scarcely perceptible in the radial artery. In the appearance of the patient there is nothing but slight pallor to indicate that anything unusual has happened. The tachycardia is commonly ushered in with a few premonitory intermissions and the attacks often terminate in two or three slow beats before the normal rate is established. Sometimes the tachycardia begins directly, without the slightest warning, in the form of several irregular beats.

Patients who suffer from reflex tachycardia are constipated and gener-

ally suffer from insomnia. The common sequence of events is first the constipation, then insomnia, which after a few days is followed with an attack of tachycardia. The use of alcohol, tobacco, tea, and coffee are undoubtedly contributory factors in many cases. One patient, a woman aged forty years, whose first attack of tachycardia occurred in her eighteenth year, developed an arhythmia on one occasion which clearly originated from the œsophagus and cardiac end of the stomach. She had sour eructations from the stomach for several days, and one evening she noticed that every time she swallowed the heart would intermit. This reflex inhibitory influence on the heart originated through centripetal stimuli from the superior laryngeal and œsophageal branches of the inferior laryngeal. The vagus centres were in an abnormally irritable state to respond in this manner to stimuli which ordinarily have no effect on the inhibitory vagus centres. She was unable to eat or drink anything that evening, and went to bed with her head turned to one side and a towel tucked under the corner of her mouth to catch the saliva. Every time she swallowed the collected saliva her heart would intermit. The symptom lasted until the following morning. Gastric lavage was then performed and the tube was swallowed without causing any intermission in the heart beat. The patient lay on the right side during this procedure, and when she turned on her back or to the left side while there was a pint of water in the stomach the heart would intermit.

There is no association between any qualitative or quantitative disturbance in the gastric secretion and these attacks of tachycardia, so far as could be ascertained in the cases under observation. If the patients have free passages from the bowel, have restful sleep at nights, and are not tired by any undue physical or mental work or emotional excitement, they are quite free of their trouble.

The effect of distension of the stomach from gas or food is well recognized in the course of diseases of the myocardium, the heart valves, and the aorta. It is not uncommon to find acute dilatation of the heart in old myocardial and valvular lesions which is caused by constipation and meteorism. So, also, is cardiac pain in disease of the aorta directly dependent on the ingestion of a very moderate amount of food, when the increased work put on the heart by the demands of digestion could not possibly be the source of the pain. The routine practice, in treatment of acute myocardial incompetence in chronic diseases of the heart muscle and valves, is rest in bed and saline cathartics, postponing the use of digitalis until it is known whether the salines may give the desired relief. Lowering the blood pressure is not the only source of relief from the use of cathartics. The cardiac patient complains of anorexia, palpitation, arhythmia or cardiac pain when compensation is well maintained, so that the digestive trouble cannot be accounted for by stasis. Diminution in the area of dulness of an enlarged heart is mentioned by Fraentzel[1] as commonly following relief from constipation. The same writer mentions the precautions taken at health resorts where springs of carbonated water are visited by patients. Patients with cardiac diseases are cautioned

[1] *Idiopathische Herz Vergrösserungen*, Berlin, 1892.

against drinking water highly charged with carbonic acid, because early in the history of these springs many cases of sudden death occurred when the patients drank freely of carbonated water.

All patients with heart disease find they are much freer from discomfort when they put only a small bulk of either solids or liquids in their stomachs and have free movements from the bowel. But the margin of tolerance in these patients is so small, even when the heart is in a fairly good state of compensation, that it does not seem reasonable to explain the pain, arhythmia, dilatation, and even sudden death by added work to the heart from increased resistance in the splanchnic vessels. Reflex nervous effects on these diseased hearts from the digestive tract are no more mysterious in their mode of production than the proposed mechanical method of production which is the more popular conception of this common clinical symptom. It is not unreasonable to believe that a diseased heart will alter its manner of response to reflex stimuli so that a stimulus (which under normal conditions would not affect the rhythm) may in a diseased heart elicit reactions quite different from those in a healthy heart. There does not seem to be any evidence which shows that the prolonged and oft-recurring attacks of tachycardia due to reflex causes from the stomach will cause organic disease of the heart, nor does this association of symptoms between the stomach and heart imply any acquired or congenital defect. These symptoms occur in persons over such a long term of years, with such a sound circulatory system in the interims between the attacks, that we are compelled to believe the fault lies in the centres rather than in the character of the gastric disturbance or in any cardiac defect. The arhythmia and tachycardia in such patients are known to occur often as the result of nervous exhaustion or great emotional excitement. Another proof of the psychical factor in the production of these phenomena is the great improvement which attends the conviction on the part of the patient that the trouble is really due to reflex causes and not to any disease of the heart. If these patients learn they can arrest the tachycardia by any procedure, they gain confidence in themselves and the attacks grow less severe and less frequent.

Nothnagel's conception that there existed a close analogy between paroxysmal attacks of tachycardia and epilepsy, particularly petit mal, is probably in the direction of a solution of the problem. In the case of the heart there was a temporary suspension of inhibition with an abrupt beginning and termination. But here we meet the problem of determining where the suspension of inhibition takes place. In the central nervous system or in the heart? During recent years, champions of the myogenic theory of cardiac autonomy have dominated the field so that there seemed little hope left for the proof of regulatory centres in the heart, but there is some valuable evidence in support of the neurogenic theory. Bethe[1] has shown the existence of a rich supply of nerve fibres and ganglion cells in the entire heart muscle of the frog, even fibres and ganglion cells in the apex of the heart. Carlson[2] has offered the best evidence thus far presented on the neurogenic side of the question. One must be cautious in

[1] *Allgem. Phys. u. Path. des Nervensystems*, Leipsic, 1903.
[2] *American Journal of Physiology*, 1904 and 1905.

applying the results of physiological experiments on low forms of animal life to the human heart, but Carlson's work shows that much of the support to the myogenic theory from observations on lower forms of animal life has not been correct. He furthermore has shown the dependence of the heart of the limulus on its nerve ganglia for both its autonomy and coördinated contraction of various portions of the heart. Inhibitory influences on the limulus heart from ganglia of the abdominal cord are exercised through the medium of the heart ganglia and not directly on the heart muscle. If one applies these results to the human heart, the evidence is very strong that cardiac autonomy and coördination are dependent on the intracardiac nerve centres and fibres. The heart stimulus is constant, but rhythmically interrupted. This rhythmic interruption or inhibitory influence persists in the after-living human heart, which recovers its rhythmic contractions many hours after removal from the body when the coronary arteries are irrigated with an appropriate serum. In the light of this experiment it is not at all to be wondered at that tachycardia cannot be produced by any experiments on the extracardial nerves.

The inhibitory centre lies within the cardiac ganglia and to produce the "cardiac epilepsy, or petit mal," which Nothnagel terms tachycardia, the suspension of inhibitory influences may take place in the intracardiac ganglia and not in the bulbar ganglia cells. Stimulation of the accelerator nerves and section of the inhibitory nerves fail to produce tachycardia. Tachycardia may be produced by continued stimulation of the atrioventricular bridge, so that the attempt to arrive at a solution by exclusion is blocked by the question whether tachycardia is due to stimuli which pass through undiscovered paths to the accelerator fibres, or to suspension of the intracardiac inhibition. If reflex tachycardia is due to a suspension of inhibitory influences, it seems evident that this must be accomplished through influences on the intracardiac nervous structures which are now found, at least in some animals, in great abundance where they were formerly believed to be absent.

Tachycardia from reflex gastric disturbances may often be checked by a hypodermic injection of morphine, but essential paroxysmal tachycardia from myocardial disease is unaffected by morphine. This has been the writer's experience, and, so far as can be determined, is the general experience. This method is not justifiable in the treatment of reflex tachycardia, because neurotic patients (with whom we have to deal) are too easily taught to resort to morphia.

In *reflex* tachycardia the most efficient treatment is to induce eructations of gas by giving Hoffman's anodyne in 0.5 dram (2 cc.) doses with sugar or water, or by giving bicarbonate of soda (a teaspoonful dissolved in a half-glass of water). In some attacks there is no apparent association between the accumulation of gas in the stomach and the tachycardia. Cessation of tachycardia is not marked by escape of gas through the cardiac orifice or through the pylorus. Compression of the abdomen by drawing on the ends of a broad towel wrapped about the abdomen or inverting the body, thus emptying the splanchnic vessels and at the same time stimulating the medullary vagus centres, are the best methods of arresting the attacks, because such methods convince the patient of the

purely reflex character. When this is once thoroughly impressed on the patient's mind, much is won toward preventing a recurrence of the attacks, and should they recur the patient is not thrown into a panic from fear of sudden death. A tranquil mental state assists in combating the individual attacks and aids much toward warding off a return of the symptom.

Although bradycardia can be produced experimentally by distending the stomach of an animal, and was produced in the human subject in the manner above described, it is not the form of reflex neurosis of the heart commonly seen. In neurasthenia and hysteria, bradycardia is seen in conjunction with nervous dyspeptic symptoms, and is usually accompanied by anesthesia of the larynx and pharynx, narrowing of the visual field, and regional anesthesia of the skin. In von Noorden's cases the heart rate could be still further reduced by suggestion. Paroxysmal bradycardia associated with disturbances of gastric digestion is of longer duration than tachycardia from the same source. In an instance in a young woman, aged twenty-four years, the attacks lasted as long as two days, but during this time there was rarely any irregularity. The pulse rate was 50 per minute and the character of the pulse and heart impulse was a reproduction of the pulse and precordial impulse which accompany vagus irritation. While the bradycardia lasted she went about her usual occupations and complained only of the uncomfortable throbbing over the heart and in the carotid arteries. The gastric disturbances in these attacks were manifested by sour eructations, although there was not a great amount of gas in the stomach or the bowel. Bicarbonate of soda gave some relief, but there was not a prompt return to the usual heart rate of 76 per minute after the eructation of gas, as usually occurs in attacks of tachycardia.

The act of vomiting in children causes slowing of the heart rate and cardiac intermissions, signs which may arouse suspicion of beginning tuberculous meningitis. In such cases the cardiac inhibition originates from the œsophagus and the region supplied by the superior laryngeal. Depressor irritation from the superior laryngeal is a phenomenon with which we are perfectly familiar, from many clinical experiences and experimental confirmation.

In paroxysmal bradycardia of reflex origin or constant bradycardia of nervous origin, atropine in sufficient amounts to reduce the vagus inhibitory tone will relieve the symptom, but will not protect the patient against subsequent attacks.

SEXUAL ORGANS AND THE HEART.

The pelvic organs and external genitalia have a rich sympathetic nerve supply from the inferior hypogastric plexus, which is a continuation of the solar and aortic plexuses. There is also a direct connection between the renal plexus and the ovaries. Vasomotor depression and accelerator impulses to the heart are very common manifestations associated with irritation of the pelvic organs in both male and female. Vasomotor disturbances and increase in the heart rate are very much more common than inhibitory influences and intermission in the heart ryhthm.

Paroxysmal vasomotor depression follows the act of coitus in some men, so they are compelled to keep in a horizontal position for several minutes until the vasomotor tone recovers. Elderly men who marry young women are commonly known to develop myocardial insufficiency. Instances of death from angina pectoris during coitus have occurred in persons who have disease of the valves or coronary arteries and myocardium.

There is great difficulty in learning all the factors which are responsible for exhaustion and cardiac symptoms in cases where excessive coitus is supposed to be the underlying cause. This is almost invariably combined with abuse of tobacco and alcohol, insufficient sleep, and gluttony. It is the combination of all these indulgences which serves to weaken a normal heart or cause dilatation of a diseased one. Fraentzel refers to several students who spent a few weeks in riotous living of this sort. At the end of a debauch both young men had clearly demonstrable enlargement of the precordial area of dulness and other signs of myocardial impairment. It would not be correct to ascribe all the symptoms to venereal excess, when gluttony in eating and excessive drinking and smoking are also implicated. Myocardial disease is commonly seen in persons who have led intemperate lives. Of all the forms of sensuous indulgences, the one oftenest enjoyed to the exclusion of all other excesses is gluttony, therefore, the one form which we most frequently see as the sole etiological factor of myocardial disease.

In some of these patients vigorous exercise increases the palpitation and heart rate to such a marked degree that the limitations in exercise permitted nothing more vigorous than walking at a moderate gait. Although the observations in certain patients tend to prove the sexual origin of the cardiac symptoms, we must use great precaution in arriving at such an opinion by exclusion of all other factors. Enlarged mediastinal glands which are not demonstrable, or the results of a former infection could produce such cardiac symptoms.

Cardiac palpitation with rapid pulse and slightly increased cardiac volume are described as results of excessive masturbation. Probably the cerebral cortex in such cases is as much the source of these symptoms as the sexual organs. Any factor which is so productive of painful mental experiences and introspection cannot be clearly differentiated as the sole cause of disturbances in the rate and rhythm of the heart. Another source of error in observations of this kind has been the interpretation of a slight increase in the volume of the heart. In the past there has not been sufficient caution exercised in differentiating between active and passive cardiac dilatation. The former kind of dilatation does not imply a myocardial defect and may result from disturbance of cardiac innervation, when the myocardium is sound.

Kisch[1] describes instances of vaginismus in married women, in which every attempt at coitus was followed by severe palpitation and tachycardia which lasted for half an hour. The pulse is described as pulsus celer with dicrotism. He refers to several instances of sudden death due to minor operations on the external female genitalia which were believed

[1] *Uterus und Herz in ihren Wechselbeziehungen*, 1898.

to have resulted from reflex stimulation of the bulbar cardiac centre. Increase of the pulse rate and arterial pressure and slowing of the heart rate and arrest of the heart beat have all been observed as effects of traction on the ovaries.

Pallor, low blood pressure, rapid heart rate, and vomiting are well-known symptoms of injuries to the testicles. Two young women, both multiparæ, neither of whom had any disease of the uterine adnexæ nor malposition of the uterus, complained of faintness after defecation. One patient was compelled to lie down for a few minutes on the bathroom floor, after a large stool, to keep from fainting. Both these patients were tall and very longwaisted, with lax abdominal walls and ptosis of both kidneys, liver, and stomach. Excessive mobility of the floor of the pelvis was responsible for traction on the pelvic structures during the act of defecation, and this produced, through irritation of the abdominal sympathetic, a transient vascular relaxation in the splanchnic vessels. Symptoms quite like those of exophthalmic goitre have been observed during the menstrual period, which ceased during the interim. There are many cases of disturbed cardiac function which are described as cured by some gynecological treatment, but it is very difficult in many such cases to know if the heart symptoms are the direct result of reflex nervous disturbances or consequent on the neurasthenia which so often accompanies affections of the generative organs.

The beginning and end of menstruation are often associated with palpitation, rapid heart, and sudden vasomotor oscillations. The symptoms appear in girls often as they commence to menstruate and cease after the menstrual periods are established. Hot flushes, palpitation, and rapid heart are symptoms most women expect at the menopause. The female insane commonly have exacerbations of cerebral symptoms at the menstrual period. Instances of paroxysmal tachycardia with a heart rate of 200 have been known to develop at a time when the menstral flow failed to appear at the proper time and the normal heart rate returned with the menstrual flow. Such cases need to be observed for a long period before a final opinion can be formed. The career of an essential paroxysmal tachycardia may begin coincidently with such an experience, and only prolonged observation of such a case would show the real significance of the tachycardia, for many of these patients go a year and more without a recurrence of the attacks.

Coitus reservatus is credited with causing disturbances of the heart rhythm and rate, but it is doubtful if this departure from the normal can in itself have any more injurious effect on the heart than other deviations from sexual rectitude.

There are many sources of error in interpreting the physiological relations between diseases of the sexual organs and reflex symptoms in the heart and vasomotor system, and though their exact physiological relations have not yet been clearly shown, it is a factor which must never be neglected in seeking an explanation for disturbances of the heart's innervation in both men and women.

IRRITABLE AND WEAKENED HEART.

Up to the present time there exists no absolute pathological and clinical proof of acute passive dilatation and death from excessive muscular exercise; although there are excellent physiological and clinical reasons for believing they occur, there always lurks the suspicion of other contributory factors in such cases, viz., a remnant of a former infection, congenital defects, or manner of living. So there has not yet been shown a completely satisfactory case with acute changes in the myocardium due to overwork. Although there exists no doubt of the ability of a man to work a heart which is impaired to death, there is some doubt about a sound heart being worked to death. This is a purely relative matter between the endurance of the skeletal muscles and the endurance of the myocardium. An athlete starts on a mile run; during the first quarter his heart beats more violently and his dyspnœa distresses him more than in the second quarter. He has caught his second wind. This experience is due to the intervention of depressor-nerve stimuli which introduce vagus influences for the conservation of the heart and vasomotor relaxation to lighten the vascular resistance. It is probably this vagus influence which causes the compensatory active dilatation in muscular exercise which has often been falsely interpreted as a passive dilatation and sign of the heart failing under the increased demand of physical exertion.

The vagus is the diastolic and anabolic nerve of the heart, and both influences are conservation measures under such circumstaces. The heart is capable of greatly increasing its capacity without causing passive dilatation, and the anabolic effect of vagus influences affects the metabolism of the heart muscle in a favorable manner. The accelerator nerves are the katabolic nerves of the heart. In paroxysmal tachycardia the heart really diminishes in size in an attack. If the attack is prolonged for several days we then see signs of passive dilatation appear. The heart increases in size and cyanosis, dyspnœa, pulmonary œdema, hepatic stasis, albuminuria, and œdema of the legs develop. These signs have been observed to reach a point where it seemed death was imminent, when suddenly the normal rhythm of the heart was restored and all signs of incompetence promptly disappeared. Such a series of events followed by instantaneous recovery would be impossible if the tachycardia were merely a symptom of myocardial disease and not the primary affection. In such a case we are justified in saying the heart exhaustion is due purely to accelerator influences.

The accelerator nerve influences are katabolic in character. If tachycardia alone can produce acute passive dilatation, how much more reasonable is it to believe that such may occur after prolonged and severe muscular exercise, when the blood is loaded with the products of metabolism from the muscular system and the heart's work is magnified by the enormously increased mass movement of the blood. It must be remembered that the increase of the heart's rate from exercise is due to accelerator stimulation, and this is associated with katabolic processes in the heart muscle. The effect on the heart from maximal physical exertion outlasts the effort by several hours. Observations on bicycle riders have shown

the heart rate to be still rapid as long as five hours after the exercise. These athletes show more weakened and irritable hearts than any others. This is due partly to the fact that the exercise is adopted by so many persons with widely different physical resistance and the illusory charm about bicycling which makes the rider underestimate the work he is performing. Elie de Cyon[1] suggests that the attitude of the bicycle rider causes compression of the abdomen to such a degree as to overbalance the compensatory vascular relaxation which follows centripetal impulses through the depressor nerves.

The first publications which called the attention of the medical profession to physical exercise as a cause of heart disease were those of Peacock in England in 1865 and Da Costa a few years later in America. Peacock studied the cases of heart disease among the miners of Cornwall who worked in a stooping position in a vitiated atmosphere, and Da Costa studied the functional impairment of the heart (unassociated with any demonstrable lesion of the heart or arteries, which he found in soldiers during the Civil War. Da Costa's[2] cases of "irritable heart" represent a class which, of course, do not come to anatomical examination as a result of the heart affection; so that the real condition of the myocardium in such cases is unknown. From the consideration of the heart's work and its relation to metabolism in the myocardium it does not seem justifiable to regard these symptoms as a neurosis. None of Da Costa's cases were associated with physical exercise alone. Both the mental and physical hardships of army life were necessarily combined and other contributory factors were also in evidence. Typhoid fever, dysentery, excessive chewing and smoking of tobacco, alcohol, and disturbance of the sexual organs are all mentioned in connection with the hardships of campaigning and camp life. These patients had a continuously rapid heart rate and precordial pain which were much increased with exercise. The physical endurance of these men was not equal to the duties of army life, but after prolonged rest they recovered from their symptoms.

Symptoms.—Precordial pain and rapid heart rate are the two conspicuous symptoms in the irritable heart. The writer has seen these symptoms persist as long as two years in a man, aged forty-five years, who otherwise was in perfect health before the occasion which gave rise to the trouble, and he has continued to enjoy perfect health for several years since the symptoms subsided. This man (to board a train) walked a mile at the top of his speed, wearing a heavy overcoat and carrying a heavy travelling bag in each hand. He was seized with violent pain over the lower end of the sternum and over the heart to the left of the sternum when he arrived in the car. Dyspnœa and cough with expectoration of thin mucus lasted for half an hour. There was slight pain over the heart continuously present, and this was accentuated on very moderate exercise for nearly two years after this experience. The sounds of the heart were normal, but the area of dulness extended one-half inch to the right of the sternum and to the left to the nipple line. The heart rate was never below 80 when he was at rest. Several years later all the symptoms,

[1] *Les Nerfs du Cœur*, Paris, 1905.
[2] *Am. Jour. Med. Sci.*, 1875.

both subjective, and objective, were no longer present. This man had nothing in his personal history which could assist in producing the symptoms.

Such symptoms occur in nervous persons who are subjected to marked vasomotor contractions and who suffer from atonic distension of the stomach and constipation. These persons are not capable of normal physical endurance because of a genuine cardiac impairment, but they are often treated too lightly because of the lack of very pronounced physical signs. Under the head of "irritable" or "weakened" heart are found cardiac disturbances which may have varying etiological factors. Whether the original cause be purely nervous, some infectious disease, intoxicants, or physical exercise, they all have the effect of reducing the heart's capacity for work, and that, after all, is the one essential thing for the physician to recognize. If the symptoms have been brought on by overexertion, prolonged rest, massage, baths, and graduated exercises against resistance should be employed. The character of the diet should be regulated to prevent gastric and intestinal fermentation and constipation. The patient must be cautioned against the danger of overexertion and the use of coffee, tea, alcohol, and tobacco. By observing precautions of this sort, the later development of permanent myocardial disease can be prevented, a probable result if the patient were taught to regard his discomfort as an emanation from his inner consciousness.

Tea and Coffee.—The effect of caffeine on the mammalian heart has been interpreted in as many different ways as there are students of the subject. The most complete study from laboratory experiments is that of Santesson (cited by Heinz).[1] Santesson found that caffeine in moderate doses increased the pulse rate, the arterial blood pressure, and the pulse volume. The increase in the pulse rate is independent of the intracardial nerves and is due to the effect on the seat of the automatic stimulus in the heart itself. The increase of the blood pressure is due to two factors, viz., vasomotor contraction and an increase of the pulse volume. These findings are quite in accord with clinical experience. In toxic doses caffeine causes arhythmia and ultimately the auricle contracts more frequently than the ventricle.

When coffee is drunk in moderation, it may be responsible for occasional cardiac intermissions, but it is very doubtful if this can be a direct effect. It is more probably a reflex effect on the heart due to disturbances in the stomach digestion. Tea and coffee certainly favor the production of paroxysmal tachycardia in patients who have such attacks secondarily to gaseous distension of the stomach.

An instance of excessive coffee drinking associated with marked disturbances of the heart's volume and rhythm occurred in a woman aged forty-eight years, who held a very responsible position which greatly taxed both her physical and nervous strength and entailed much loss of sleep. From ten to twelve cups of moderately strong coffee had been her daily quantity for two years. The heart was enlarged both to the left and right. The apex was in the fifth interspace one inch outside the nipple line and

[1] *Handbuch der experimentellen Pathologie*, i, part ii, 975.

the right border was plainly demonstrable by percussion one inch to the right of the sternum. The sounds over the heart were perfectly clear, but the heart was very arhythmic. There was no suggestion of any form of allorhythmia. The rate varied from 90 to 110 per minute. The arterial pressure was not above the normal point and there were no signs of an increased peripheral arterial resistance. There were no signs of pulmonary stasis nor œdema of the pendent parts, but the liver was sensitive and enlarged to about three fingers' breadth below the costal border in the nipple line. Strychnine, strophanthus, and digitalis had not the slightest effect on the rate or rhythm of the heart. After a month's rest in bed with a mixed diet, which was taken in small amounts every three hours during the day, coffee being discontinued, the heart rate became slower and less irregular. The dimensions of the heart diminished, but did not return to the normal size. The liver was no longer sensitive and resumed the normal size. The patient adopted a hygienic mode of living and was able to continue her work with little discomfort, although the arhythmia and slight cardiac enlargement were present a year later.

This is a rare and extreme instance, but shows how anatomical changes may be produced in a heart from prolonged and excessive coffee drinking. Tea and coffee may cause cardiac symptoms either indirectly through reflex disturbances from gastric dyspepsia or directly by excitation of the vasomotor centre and the myocardium.

CHAPTER X.

CONGENITAL CARDIAC DISEASE.[1]

By MAUDE E. ABBOTT, M.D.

Definition.—Congenital cardiac disease may be defined as that condition in which, through arrest of development or disease occurring in intrauterine life, anomalies in the anatomical structure of the heart or great vessels exist, leading to irregularities in the circulation. It is frequently associated with congenital cyanosis and clubbing of the fingers, and constitutes in extreme cases the *morbus cæruleus* of the older writers.

THE DEVELOPMENT OF THE HEART.

It is impossible to approach this subject intelligently without a certain preliminary knowledge of the development of the mammalian heart. A brief statement referring especially to the development of the septa, the involution of the bulbus cordis and sinus venosus, and the disappearance of the primitive aortic arches, is therefore necessary here. For fuller details the reader is referred to the fundamental studies of His[2] and Born[3] and to the recent contributions of Tandler,[4] Mönckeberg,[5] and Mall.[6]

The mammalian heart is formed originally of two straight tubes placed independently on either side of the body, which merge together as the ventral cleft closes in and finally fuse, the septum thus formed becoming entirely obliterated before the permanent interventricular septum begins to appear. Meanwhile a twisting of the heart upon its long axes occurs, and it becomes no longer symmetrical, but S-shaped, with the ventricular portion bent forward and downward and the auricular part upward and backward. It now consists of two chambers, a single ventricle forming its anterior and lower part with its bulbus cordis passing upward and to the left and *giving off the aortic trunk from its right angle* (Figs. 16 and 17), and a single auricle with its sinus venosus lying behind and to the left. At this stage it resembles the two-chambered heart of the fish, and is especially interesting in regard to the formation of the bulbus cordis.

[1] This article has been largely rewritten, and curtailed in parts, to permit of the addition of new material, especially under the Development of the Heart, Anomalies of the Pericardium, Dextrocardia, Congenital Rhabdomyoma, Auricular, Ventricular, and Aortic Septal Defects, Deviation of the Aortic Septum, and Patent Ductus Arteriosus. The reader is referred to the earlier edition for the omitted material.

[2] *Beiträge zur Anatomie des menschlichen Herzens*, Leipzig, 1886.

[3] *Beiträge zur Entwickelung des Saugethierherzens*, Arch. f. mikr. anat., 1889, xxxiii.

[4] *Keibel and Mall's Human Embryology*, 1912, ii, pp. 534–570.

[5] *Atlas der Herzmissbildungen*, Jena, 1912; also, Verh. d. Deut. Path. Gesell., Marburg, 1913, xvi, p. 228.

[6] *Am. Jour. Anat.*, 1913, xiv, p. 249.

The auricle next shifts upward, coming to lie above the ventricle, and its auricular appendages develop enormously, pouching forward on either side of the bulbus (Fig. 19). The atrial canal, in which are developing the

Fig. 16

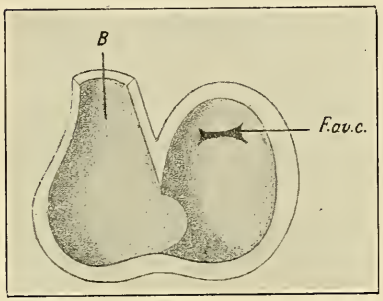


Fig. 17

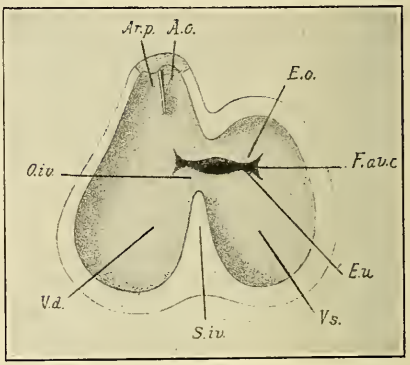
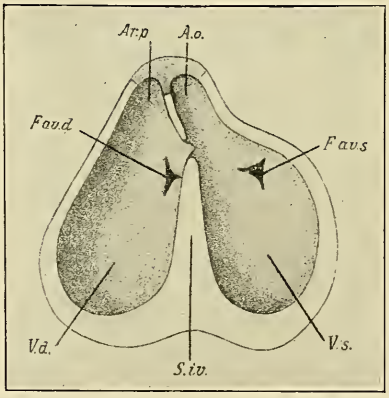


Fig. 18



The separation of the ventricles. (After His.)

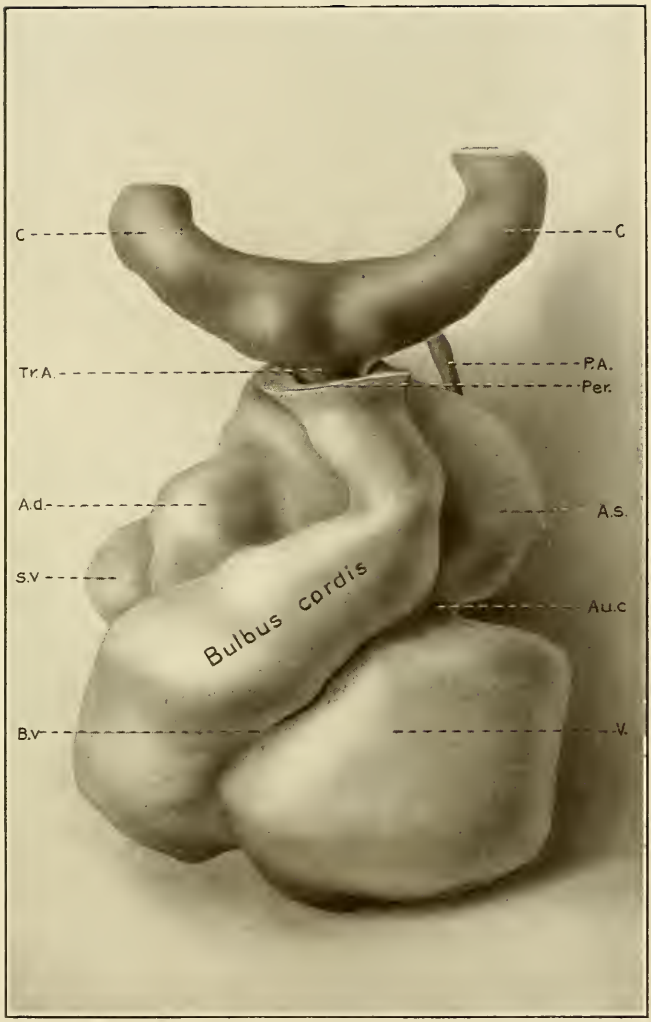
Fig. 16.—Embryo 1.9 mm. long. The single ventricle gives off the common arterial trunk (*B*) from its *right* upper angle, and receives the common auriculoventricular orifice (*F.au.c.*) entirely on its *left* side.

Fig. 17.—Embryo 3.5 mm. long. The common trunk has moved somewhat to the left and is divided by the aortic septum. The interventricular septum (*S.iv.*) divides the ventricle into two parts, leaving the interventricular foramen (*O.iv.*) still open above. The auriculoventricular orifice (*F.au.c.*) has moved to the right, so that part of it lies in each cavity. *E.o.*, upper endocardial cushion; *E.u.*, lower endocardial cushion; *V.d.*, right ventricle; *V.s* left ventricle.

Fig. 18.—The aortic and interventricular septa have united, and completed the division of the ventricles. The pulmonary artery (*Ar.p.*) arises from the right, the aorta (*Ao.*) from the left ventricle, and the right and left auriculoventricular ostia (*F.au.d.*, *F.au.s.*) lie in their respective cavities. *V.d.*, right ventricle; *V.s.*, left ventricle; *S.iv.*, interventricular septum. (From Vierordt, Nothnagel's Series, xv, 1–2.)

endocardial cushions which are to separate the two venous ostia, has become elongated and still opens into the common ventricle entirely on the left side. The sinus venosus is now a separate cavity opening into the auricle on its right wall posteriorly through a narrow cleft, the edges of

PLATE V



Model of the Heart of a Human Embryo 4.6 mm. long x 108.
F. T. Lewis and M. E. Abbott. (Dr. Begg's Embryo.)

(*From the Anatomical Laboratory of the Harvard Medical School.*)

C., carotid arch; *P.A* , pulmonary artery; *Per.*, pericardium; *Tr.A.*, truncus arteriosus; *A.d.*, right auricle; *A.s.*, left auricle; *S.v.*, sinus venosus; *Au.c.*, common auriculoventricular orifice; *B.v.*, bulboventricular cleft; *V.*, common ventricle.

which project into the auricle as the valvulæ venosæ dextra et sinistra. At its upper border it is elongated laterally into the two sinus horns which receive the two superior venæ cavæ, while a single short trunk, the inferior cava, enters it below.

The Bulbus Cordis.—This name is given to a transitory portion of the embryonic heart leading from the right end of the common ventricle to the aortic arches. In the human embryo of 4 to 6 mm. in length the bulbus is a thick-walled muscular tube passing to the left and upward, lined like the rest of the heart with endothelium, which presents certain endocardial thickenings, *spirally arranged* (Tandler), the so-called proximal and distal bulbar swellings, structures which later form the *anlagen* of the semilunar cusps as well as of the lower part of the aortopulmonary septum. In later stages the bulbus disappears, its proximal portion being taken up in the wall of the ventricle, and its distal part, denuded of its musculature and considerably elongated, constituting the primitive aortic trunk. The researches of Greil[1] on the reptilian heart, and Keith,[2] and recently of Jane Robertson[3] on the fish, show that the mammalian bulbus represents what was at one time an independent chamber with muscular walls and its own system of multiple valves, which in the "ontogenetic telescoping of phylogenetic stages" has become submerged.

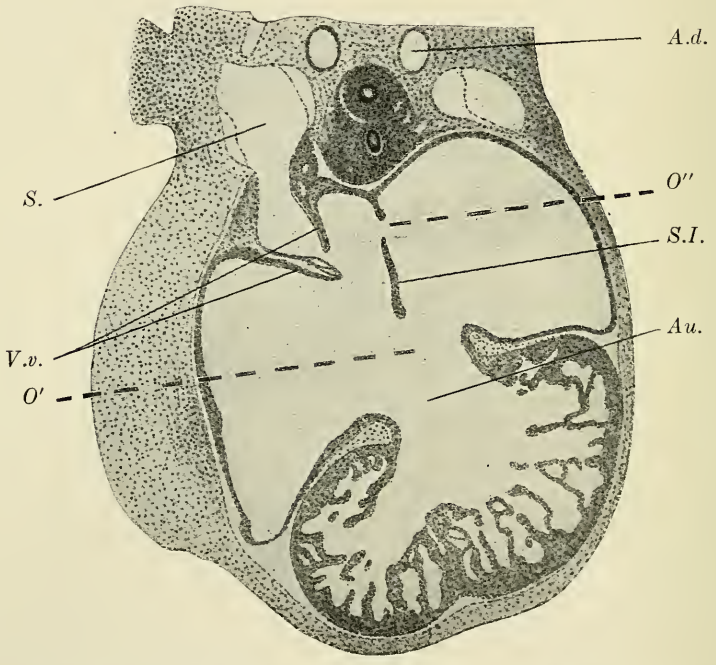
Robertson correlates her findings in the fish with those of Greil in the lizard, and Born in the mammalian embryo, and traces the bulbus of the latter back through the less blurred stages of the reptile to the simpler forms seen in the Dipnoan and Elasmobranch fishes. Thus this structure, represented in the adult mammal, with its fully established double circulation, by the completely separated aortic and pulmonary trunks, is seen in *Lacerta* (reptile) to consist of a curved muscular tube divided by a spiral aortopulmonary septum, which gives way in turn in *Lepidosiren* (Dipnoan fish) to a kinked muscular tube with median expansion incompletely divided by rows of spirally arranged valves, and this again in the Elasmobranch fishes with their purely branchial respiration, is reduced to the simplest form as a straight channel with muscular walls lined by numerous rows of longitudinally placed valves. These phylogenetic proofs of an early bulbar channel with spiral division of its distal portion, are of the utmost importance in the elucidation of the problems of stenosis of the pulmonary conus and transposition of the arterial trunks, and yield striking confirmation of the explanations offered by Keith of the former, and by Rokitansky of the latter anomaly.

The Interauricular Septum.—Born showed that the division of the auricles takes place through the development of *two different partitions* placed in planes parallel with each other developing successively, parts of both of which are temporary, while parts persist to form the permanent interauricular septum of postnatal life. Of these septa, the one developing earlier, called by Born the *septum primum*, begins about the fourth week from the upper and posterior wall of the auricle as a sickle-shaped fold which grows forward and downward toward the ventricular cavity, and

[1] *Morph. Jahrb.*, 1903, xxxi, p. 123.
[2] *Festschrift of the Quatercentenary of Aberdeen University*, July, 1906.
[3] *Jour. Path. and Bacteriol.*, 1913, xviii, p. 191.

for some time an opening exists between the auricles at the lower border of this primitive septum known as the *ostium primum*. About the beginning of the fifth week a second opening, called by Born the *ostium secundum*, forms in the now greatly thinned upper and back part of the septum primum. This second opening grows larger as the ostium primum becomes smaller, and finally disappears entirely (end of fifth week), through the union of the expanded lower margin of the septum primum with the fused endocardial cushions between the auriculoventricular ostia. There thus exists a stage in development when the septum primum is represented by a band of tissue between two orifices, the ostium secundum above, and the ostium primum below. (See Figs. 19 and 20.)

Fig. 19



Transverse section through the heart region of an embryo of 8 mm. greatest length. *A.d.*, descending aorta; *Au.*, atrial canal; *S.*, sinus venosus; *V.v.*, valvulæ venosæ; *S.I.*, septum primum. Note the bifid apex seen at this stage and also the presence of two openings (O′ and O″) in the primitive auricular septum. In the collection of the I. Anatomical Institute, Vienna. (From Tandler's article in Keibel and Mall's Embryology, vol. ii, p. 549.)

The *septum secundum* arises considerably later than the septum primum in a plane a little to its right, from the upper wall of the right auricle, and passes downward covering in the upper and anterior portion of the ostium secundum, thus giving it a valvular character, and transforming it into the foramen ovale of fetal life. A portion of the septum secundum persists in adult life as the *annulus ovalis*, while the *valvula foraminis ovalis* of the adult left auricle represents the remains of the primary septum, the primary and secondary ostia of which have both become obliterated.

The Interventricular Septum.—This begins about the fourth week, just after the origin of the auricular septum, as a crescentic ridge on the inferior wall of the ventricle. It grows upward and backward, its posterior limb merging with the corresponding walls of the ventricle and with the posterior endocardial cushion, and its anterior limb with the anteroventricular wall along the bulbo-atrial ridges, while its median curved portion unites with a prolongation of the proximal aortic septum (the aortic orifice having moved over from the right to over-ride the ventricular septum), and with the fused endocardial cushions of the auriculoventricular orifice (which has also come to lie in the median line), so that the ventricles are completely separated from each other and the arterial and venous ostia are placed one in either ventricle (Figs. 17 and 18). The point of union of the aortic with the interventricular septum just below the adjacent ends of the anterior and left posterior aortic cusps, remains transparent and devoid of muscle throughout life, and is known as the *pars membranacea*, or undefended space.

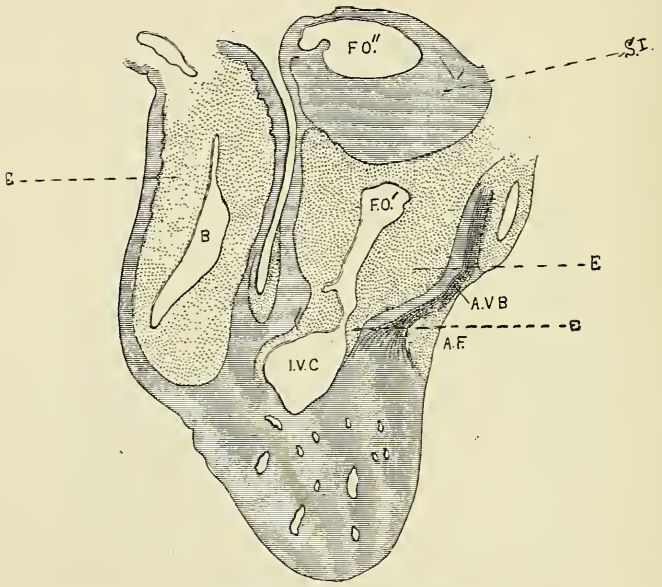
The Aortic Septum.—The *truncus arteriosus* is divided into the two great efferent vessels of the heart by a septum derived from three sources. Before the fifth week a sharp fold, the *aortopulmonary septum proper*, appears in the lumen of the truncus at the point of junction of the 4th and 6th arches (which represent respectively the aortic and pulmonary trunks) and grows rapidly downward. Some distance above the heart this aortopulmonary septum proper meets and fuses with *a spiral septum derived from fusion of the so-called distal and proximal endocardial bulbar swellings.* The bulbus cordis which forms, as stated above, by the involution of its proximal portion the termination of the ventricle, and by the elongation and demuscularization of its distal portion, the first part of the primitive aorta, is supplied internally with a series of endocardial elevations, of which four belong to its distal and two to its proximal part (known respectively as the Distal Bulbar Swellings 1, 2, 3, and 4, and Proximal Bulbar Swellings A and B of Born). These swellings, while symmetrically placed on opposite sides of the tube, have a spiral arrangement from above downward, and the distal swellings 2, and 4, which are much more prominent than the distal swellings 1 and 3, are directly continuous in clock-wise spiral fashion with the proximal swellings A and B. Fusion with each other, first of the more prominent pair of the distal bulbar swellings and later of the proximal ones occurs, the *spiral bulbar septum* resulting, uniting at its distal end with the aortopulmonary septum proper, and the two structures being clearly distinguished from each other by their distinctive histological characters.

The chambers of the heart and the two great arteries have thus been completely separated from each other before the eighth week of fetal life. Meantime, the right horn of the sinus venosus has been taken up in the wall of the right auricle, and the valvula venosa sinistra has disappeared, a portion of the valvula venosa dextra persisting as the *Eustachian valve*, and the left sinus horn remaining as the coronary sinus, while the left duct of Cuvier becomes obliterated (left superior vena cava). The pulmonary veins form later, opening at first as a single trunk, which is later taken up in the wall of the left auricle, thereby enlarging it. The semilunar cusps

appear to form about the seventh week, from the proximal ends of the four distal bulbar swellings, two of which are subdivided in the descent of the septum trunci, so that six cusps, three placed in each artery, result.

The Auriculoventricular Cusps and the Atrioventricular Bundle of His. —The most critical point in the developing heart is undoubtedly the atrial canal. The endocardial cushions, which develop within it, are extensive and vitally important structures, not only as taking the essential part in the formation of the venous ostia, but also as completing the separation of all four chambers by fusion with their respective septa. Moreover, from the observations of Mall on a large series of early human embryos, we learn that the differentiation of the auriculoventricular bundle of His

Fig. 20



Sagittal section through the heart region of an embryo 8 mm. long, × 40, No. 113 of Prof. Franklin P. Mall's collection. *B*, bulbus cordis; *A.V.B.*, auriculoventricular bundle; *A.F.*, annulus fibrosis; *I.V.C.*, interventricular canal; *F.O'.*, ostium primum; *F.O''.*. ostium secundum; *S.I.*, septum primum; *E*, endocardial cushions. Note the extensive development of the endocardial cushions within the auricle. (From the article by F. P. Mall in the *American Journal of Anatomy*, July 15, 1912.)

is to be traced to the breaking of the continuity of the atrial with the ventricular musculature by the ingrowth of constricting epicardial connective tissue about the external surface of the atrial ring. Thus while in very early stages the muscle of the auricle is continuous with that of the ventricle at all points, in later stages a single band of atrial tissue passing down posteriorly from the lower border of the sinus venosus to the ventricle, and two minor fasciculi on the anterolateral wall, are the only remaining connection between the chambers. The survival of these isolated portions in the general destruction of the muscular continuity between auricle and ventricle is explained by Mall by the anatomical relations of the posterior part of the interventricular septum, which, growing

up toward the posterior endocardial cushion, pushes the epicardial tissue obliquely before it and permits the escape of a small portion of auricular muscle. This surviving atrial tissue, now the only path of conductivity, undergoes differentiation and later, innervation, and becomes readily identified as the auriculoventricular bundle.

This contention of Mall, that the bundle represents persistent atrial tissue, and that its survival at this point is the result of its anatomical relation with the interventricular septum, has received striking confirmation from the investigations of Mönckeberg, and Sato[1] in the distribution of the bundle in various cardiac defects.[2] Thus in a *Cor Triloculare Biatriatrum* where, in the entire absence of ventricular septum one might conclude a destruction of auricular tissue in the whole circumference of the atrial ring, this bundle was found to be absent from the normal situation and was represented by a small band of tissue accompanying a small vessel on the anterolateral aspect of the heart. In defects of the interventricular septum at the base on the other hand, in which the posterior part of the septum practically always remains entire, the bundle was seen intact in both ventricles, streaming over the lower border of the defect.

The auriculoventricular cusps are formed from the endocardial cushions of the atrial canal. These cushions are a series of elevations of the lining endothelium of the cardiac tube formed by a spongy connective tissue, and are four in number. Two, the anterior and the posterior, develop very early, become of large size, and, growing toward each other, fuse to form the wedge-shaped block which separates the venous ostia and completes the cardiac septa. In addition they encroach by their rapid growth on adjacent structures, so that they come to line the lower border of the *septum primum* in the auricle, while extending also by their apices into the depths of the ventricle. The lateral cushions, of smaller size, develop later, and, with the anteroposterior pair, are converted from endocardial structures into the musculotendinous valves, by the undermining of their substance from without, and by their own invasion of, and fusion with, the spongy musculature of the ventricle.

Primitive Aortic Arches.—After considerable discussion, it is now fairly demonstrated that these number six instead of five, as Rathke described, the disputed fifth arch being rudimentary in character. They are more or less evanescent in all animals, except fishes, in which five persist. In birds and mammals the first, third, and fifth disappear on both sides. In man the fourth left arch becomes the aorta, the fourth right, the right subclavian, while the sixth pair become the pulmonary arteries.

LITERATURE.

The rarity of cardiac defects, the obscurity of their etiology and symptoms, together with the fact that the cases are often of serious clinical import, make the subject of congenital cardiac disease of the highest

[1] Aschoff, *Ber. d. Naturfor. Gesell. zu Freiburg*, December 3, 1913, B. xx.

[2] Professor Adami informs me that this idea of the persistence of the primitive atrial tissue in the Purkinje fibres of the adult heart was suggested by Gaskell in his book on the *Evolution of the Vertebrates* (1904).

interest. Since the time of Senac[1] it has attracted the interest of many of the ablest workers in the field of cardiac pathology. There are important special contributions from nearly all the earlier writers upon the heart, including Morgagni, Wm. Hunter,[2] Meckel,[3] Louis,[4] Farre,[5] Breschet, Sir James Paget,[6] Gintrac,[7] Chevers,[8] and Rokitansky.[9] The first comprehensive study of the whole subject with a review of this earlier literature, may be said to be Peacock's,[10] which remains a classic and is still the leading authority in English upon the subject. In Germany the ground has been covered by Lebert-Schrötter[11] (1879), by Rauchfuss[12] (1878), by Vierordt[13] (1898), in a statistical study of great value, and more recently by Thorel[14] (1903 and 1911), and Herxheimer[15] (1910). In English there are the excellent general accounts of Humphry,[16] Carpenter,[17] and Keith,[18] and in French the work of Moussous,[19] Gérard,[20] and Thérémin,[21] The last is a study of much value comprising 106 observations of cardiac defects with measurements and illustrative plates.

Perhaps the most valuable and certainly the most brilliant original contribution has been Rokitansky's. This is an analysis of 44 cases of complicated septal defects, together with a study of the normal anatomy of the septa, and of their development as observed by Rokitansky himself, in the human embryo and in the chick. Rokitansky explained all cardiac anomalies associated with septal defects as due to arrest in the development of the cardiac or aortic septa, and to their consequent non-union or irregular union. Although the results of his observations have been modified, his work is of inestimable value as giving a clue to many problems, and especially in regard to transposition of the arterial trunks.

Reference has already been made to the recent work of Keith. From a series of personal observations on conus stenosis, and from the study of 270 malformed hearts in the museums of London, he has advanced the view that cardiac defects are nearly always developmental in origin, that pulmonary stenosis is usually due to subinvolution of the bulbus cordis and that transposition results from an irregularity in involution of the same primitive structure.

[1] *Traité de la structure du cœur, de son action et de ses maladies,* Paris, 1749.
[2] *Medical Observations and Enquiries,* London, 1784, vol. vi, p. 291.
[3] *De Cordis conditionibus abnormibus, Dissertation,* Halle, 1802.
[4] *Mémoires ou recherches anatomico-pathologiques,* Paris, 1826.
[5] *On Malformations of the Human Heart,* London, 1814.
[6] *Edinburgh Medical and Surgical Journal,* 1831, vol. xxxvi, p. 263.
[7] *Récherches sur la maladie bleue,* Paris, 1824.
[8] *London Medical Gazette,* series of articles, 1845 to 1851.
[9] *Defekte der Scheidewände des Herzens,* Vienna, 1875.
[10] *Malformations of the Human Heart,* 1858 and 1866.
[11] Article in Ziemssen's *Handbuch der spec. Path. et Ther.,* Leipsic, 1879, Band vi.
[12] In Gerhardt's *Handb. d. Kinderkrankheiten,* 1878, iv, part i.
[13] *Nothnagel's Spec. Path. u. Therapie,* Bd. xv, 1898. Th. 1., Abt. 11.
[14] *Lubarsch and Ostertag's Ergebnisse,* 1 Abth., 1903, p. 585, and 11 Abth., 1910, p. 268.
[15] *Schwalbe's Missbildungen,* iii Th., iii Lief, 2 Abth., 1910.
[16] *Allbutt's System of Medicine,* vol. iv.
[17] *Brit. Jour. Child. Dis.,* 1909, vol. vi, pp. 337, 385, 433.
[18] *Lancet,* 1909, vol. ii, 359, 433, 519.
[19] *Encyclop. Scient. des aide-memoires,* Paris.
[20] *Rev. de méd.,* 1900, pp. 645 and 837; also *Jour. de l'Anat.,* 1900, pp. 1 and 323.
[21] *Études sur les affections congénitales du cœur, Paris,* 1895.

The bulk of the literature centres about three questions, which may be stated, with the theories promulgated upon them, as follows:

1. The cause of the defect. Is it developmental or due to intra-uterine disease?

2. The causation of the cyanosis so often present: Is it due to admixture of venous and arterial currents; to delayed aëration of blood; to both these conditions, or to still obscurer causes associated with changes in tissue metabolism and in the composition of the blood itself?

3. In the combination so frequently occurring of defect of the interventricular septum with stenosis of the pulmonary artery, is the septal defect secondary, due to the rise of pressure behind the stenosed orifice before closure of the fetal passages had occurred; or is it primary, the deflection of the current of blood through the defect leading to hypoplasia of the pulmonary artery through disuse? Or are both conditions the result of a common cause, an arrest or deviation or other irregularity in development?

An analysis has been made of the records of 631 cases of congenital cardiac disease which serve here as an illustrative basis. Of these, 205 have been drawn from the *Transactions of the Pathological Society of London*, a few from personal experience, and the remainder from the literature. English and American records have been consulted so far as possible, as these sources are often overlooked in previous statistical studies, which are largely Continental.

ETIOLOGY OF CONGENITAL CARDIAC DISEASE.

Cardiac anomalies may be divided, according to etiology, into two main groups: those due to *arrest of growth* at an early stage, before the different parts of the heart have been entirely formed, and those produced in the more fully developed heart by *fetal disease*.

Arrest of Growth.—From the earliest times search has been made for the underlying causes of the arrest of development manifest in cardiac malformations. Long before Darwin, Meckel, in 1812, pointed out the resemblance of certain defects to the hearts of those animals, which present in a stationary form the different stages through which the mammalian heart passes in its development, and explained them as reversions to a more primitive type.

In seeking the causes of the defect we may turn first to the study of associated anomalies. Do these occur in such frequency and constancy as to place their combination beyond the range of coincidence? And if so, may the causes leading to malformations elsewhere, such as disease and adhesions of the amnion, maternal disease, hereditary predisposition, etc., be assumed to act upon the fetal heart?

In Rokitansky's *Defekte der Scheidewände des Herzens*, among 24 complicated defects of the septum, all evidently of developmental origin, associated anomalies such as transposition of the viscera, cleft palate, etc., occurred in 8, that is, in one-third of the cases. Vierordt, in the 700 cases reviewed by him, found associated anomalies in 80 (11 per cent.). On the other hand Keith found among 23 malformed fetuses

and infants showing anencephaly, hydrocephaly, spina bifida, umbilical hernia, atresia ani, cleft palate, harelip, and stricture of the œsophagus, in 14 a malformation of the heart.

Among the 631 cases studied here, anomalies elsewhere in the body, among which may be enumerated malformations of liver and lung, asymmetry of calvarium, partial or complete transposition of viscera, harelip and cleft palate, encephalocele, gastro- and rachischisis, absence of spleen or kidney, diverticula, hypospadias, hernia, etc., occurred in 92 cases, that is, in 14 per cent. Defect of the interventricular septum was associated in Chaffey's case with imperforate anus, in Moore's with a supernumerary thumb, in Morestin's with syndactylism and absence of femur, fibula, and genitalia. A widely patent foramen ovale was combined in Berthel's case with rudimentary genitalia, and in Tylecote's with a congenital perforation of the nasal septum. Kingsley reports patent ductus with macroglossia and absence of the left kidney, and Dick a case of pulmonary artery forming the descending aorta, with the uterus bipartite, and the kidneys fused. Mental deficiency or derangement of the higher nerve centres is not infrequent. Thus idiocy was reported by Simmons, Carpenter and Rheiner, in cases of patent foramen ovale, patent ductus, and septal defect respectively, and in a biloculate heart reported by Dublizhaza, idiocy was combined with strabismus and pes varus.

Further illustrations might be multiplied, but the above suffice to show that the association of grave anomalies with cardiac defects is too frequent to be considered accidental. That the cause of both is to be sought, not so much in a hereditary predisposition, as in a diseased condition of the fetal envelopes or of the maternal tissues is evident from the facts yielded by the family history of these cases. For a history of congenital disease in the ancestry is much less common, than is one of cardiac defect or other anomaly in other members of the same generation, and evidence of infective processes or depressing influences acting within the parental organism is still more frequently supplied. In this series there was a history of congenital defect in a brother or sister of the patient in 11 cases, of rheumatism or heart-disease in the parents in 13, and of small-pox or tuberculosis in six. Congenital syphilis in the father was recorded by Jacobi, in a case of ectopia cordis, and lues whether congenital or acquired is certainly a frequent cause. Baneful influences acting upon the mother during the early weeks of pregnancy have been described, such as great trouble, ill-treatment and fright. Severe inflammation of the bladder of the mother in the third month was blamed by Habershon for the development of pulmonary atresia with septal defect, and an operation on the mother for appendicitis was noted by Royer and Wilson, in their case of incomplete heterotaxy. In not a few instances the parents had both reached advanced middle life, and in some the child was the last of a series of many pregnancies.

Difficult delivery occurred in the cases of patent ductus by Luys, Roeder, and others. Laine reported a case of aortic stenosis with septal defect from a mother aged forty-eight years, who had had four other children, of whom three were feeble-minded.

The predominating cause of the defect is thus clearly to be sought in the immediate environment of the developing embryo. It must be recognized that the early death in most cases of congenital cardiac disease prevents direct transmission of cardiac defects, which might otherwise occur, and this lessens the apparent frequency of heredity. That heredity is a factor in a certain proportion of cases is evidenced by numerous facts. The association of symmetrical polydactylism is significant when one considers the well known familial tendency of this anomaly. Of much interest also is a specimen reported by J. McCrae[1] in which transposition of the viscera and atresia of the pulmonary artery were found in the fifteenth child of a forty-six-year-old mother, who was herself of poor intelligence and had a harelip.

Fetal Disease.—Acute endocarditis was formerly claimed to be a widely acting cause of congenital cardiac disease, not only in those instances in which in the fully formed heart the traces of its presence are incontestable, but in the earlier cases of arrest of growth which were explained as due to its action upon the half-developed embryo. With the increasing knowledge of development, the trend of modern opinion is to explain the majority of cardiac defects as arrest of gro wth, dependent upon a variety of causes as enumerated above, and to class with these many cases of pulmonary stenosis and atresia, formerly thought to be inflammatory in origin. There remains a certain proportion due to fetal endocarditis, but it is impossible to state the exact degree of its influence, and it is therefore safest to divide cardiac defects into two classes, *viz.*, those in which an arrest of development from any cause has taken place, and those which show, by thickening and cicatricial contraction, that they have been produced by fetal disease after the heart has been fully formed.

The presence of thickening of the endocardium does not prove that a defect is originally due to an inflammatory process, for cardiac defects, giving rise so readily to abnormal currents and to undue strain upon the valves, are particularly liable to be the seat of future disease.

CYANOSIS.

Congenital cyanosis is a bluish discoloration of the skin and mucous membranes, characterizing the more pronounced cases of congenital cardiac disease in which there is serious interference with the circulation. It differs from the cyanosis of the later stages of acquired cardiac lesions in that it may exist for many years without any signs of cardiac insufficiency. Its constant association with the other evidences of deficient oxygenation—dyspnœa and clubbing—raises it almost to the ranks of a disease entity, and such, under the titles *Cyanopathia* or *Morbus Cœruleus*, it was long believed to be.

Pathogenesis.—The immediate causation has long been the subject of debate. It has been variously ascribed to (*a*) venous stasis, (*b*) admixture of currents, (*c*) deficient aëration, (*d*) dilatation and new for-

[1] *Jour. Anat. and Physiol.*, 1905, xl, 48.

mation of capillaries in peripheral parts of the body, (*e*) changes in the blood itself, *e. g.*, polycythemia. The last two conditions, being subordinate factors and secondary causes only, may be dismissed.

(*a*) The term *venous stasis* is used in this connection to imply obstruction to the free entrance of the blood to the lungs and the resultant back-pressure in the systemic circulation. This theory, advanced by Morgagni, has been largely accepted, but does not explain the situation completely. It is difficult to understand why a simple venous stasis should be sufficient to lead to cyanosis and yet remain unassociated with the œdema and anasarca accompanying back-pressure from other causes. And, on the other hand, the late appearance of the cyanosis in many cases of pulmonary stenosis in which, although the defect has been undoubtedly present at birth, cyanosis only supervenes after some months or years on the occurrence of some event temporarily increasing the embarrassment of the pulmonary circulation renders it evident that some other factor, in addition to the mechanical difficulties which the lesion presents, is, as a rule, needed to bring it about. A highly instructive case is published by Lafitte[1] of a young woman, dying at twenty-one years of a malignant endocarditis, who had always been dyspnœic on slight exertion but had never presented any trace of cyanosis. At the autopsy the right heart was hypertrophied and about one inch below the pulmonary valves there was a fibrous annular stenosis of the infundibular orifice which was further blocked by large recent vegetations. Peacock, in reporting a case of pulmonary stenosis without cyanosis, suggested that the absence of symptoms was due to the marked hypertrophy of the right ventricle which had succeeded in sending sufficient blood to the lungs for aëration.

(*b*) The theory that cyanosis is due to a *mingling of venous with arterial blood* (wrongly ascribed to Hunter, as Osler points out) has been sharply and apparently successfully refuted by many authorities, notably Peacock. Certain strong arguments can certainly be adduced against its universal application. The classical illustration is Breschet's case, in which the left subclavian arose from the pulmonary artery, and yet the left arm was normal, not discolored. Again, in many instances of biloculate or triloculate heart there is a complete absence of cyanosis. Thus Young[2] reports a cor biatriatum triloculare, both auricles opening into a common ventricle, from which arose the aorta and pulmonary artery, transposed and separated from each other by an anomalous septum in a man, aged thirty-six years, who showed no cyanosis until the last three years of life. Peacock quotes an almost identical case in an infant aged eight months, with only a slight blueness of the lips during dyspnœic attacks. Equally striking is a case of persistent truncus arteriosus, in which, although the blood from both ventricles entered the common arterial trunk, cyanosis was absent.

The theory of admixture of currents has been revived by Bard and Curtillet[3] in a form that has been generally accepted. They describe as *cyanose tardive* a cyanosis occurring as a terminal event, often at

[1] *Bull. de la Soc. Anat.*, 1892, vi, 13.
[2] *Med. Chron.*, Manchester, 1907–08, xiv, 96.
[3] *Rev. de méd.*, December, 1889.

the end of a long life, in cases of patent foramen ovale, when some embarrassment in the pulmonary circulation causes a raised pressure in the right heart leading to a flow of blood through the foramen and sometimes to a forced reopening when it has been closed. They quote an illustration in a man aged fifty-four years, with patent foramen, dying of bronchopneumonia. Long before this, Peacock[1] reported such a case, in a woman, aged twenty-four years, with marked spinal curvature and widely patent foramen ovale, in whom marked cyanosis set in for the first time in the last months of life.

That cyanosis may occur without admixture of currents, in the ordinary application of the term, is definitely shown: (1) by its presence in a limited number of cases of congenital pulmonary stenosis, in which the fetal passages are all closed, and (2) by the fact that the most marked pictures of cyanosis with clubbing may occur in acquired pulmonary emphysema and in bronchiectasis. But in these latter combinations lies perhaps the key to the situation. In bronchiectasis, as Thomas[2] points out, areas of loss of substance occur, and tortuous dilated capillaries with thickened walls exist, and it is readily conceived that in certain areas blood may pass from pulmonary arterioles to venules without undergoing due oxygenation by the way. In congenital cardiac disease dilatation and thickening of peripheral vessels form a part of the picture, and alterations very similar to those observed in bronchiectasis occur. In a case described by Carpenter[3] the lungs were loaded with pigment, their capillaries dilated to three times their normal size, crowded with red cells, elongated, tortuous, their walls thickened and rich in young fibrous tissue elements. Must not many red cells have passed through these thickened channels without receiving their due share of oxygen, and the blood have been thus returned, still largely venous in character, to the left heart. Viewed in this light do not venous stasis and admixture of currents become only a distinction in terms between two conditions leading alike to deficient aëration?

(*c*) *Changes in the Bloodvessels and Tissues.*—It was suggested by Carpenter that the changes produced in the lungs by the circulation of venous blood might lead to the cyanosis by creating pulmonary obstruction. Certainly a vicious circle is created but the altered capillary circulation, being itself the result of deficient aëration, can be looked upon only as a secondary cause of any symptoms it may help to produce.

(*d*) *Changes in the Blood Itself.*—The dark color of cyanotic blood has been ascribed to the great increase in red blood corpuscles which often exists. The polycythemia, however, can have no causal relation to the cyanosis, for it not only is not constant in the congenital form, but a very high blood count is consistent with an entire absence of cyanosis, as is evidenced in the polycythemia of high altitudes.

(*e*) The theory that a variety of causes, including both mingling of currents, venous stasis and pulmonary obstruction, lead to a deficient *aëration of the blood and that this is the essential element in the production*

[1] *Trans. Path. Soc.*, London, 1859, x, 108.
[2] *Zeit. f. klin. Med.*, 1901, xli, 58.
[3] *St. Thomas Hospital Reports*, 1890, xviii, 285.

of cyanosis, is formulated by many recent observers. There is abundant evidence to show that whatever the path by which oxygenation is reduced, whether by direct influx of venous blood into the arterial tree, or by obstruction to the entrance of venous blood into the pulmonary circulation the deficient aëration resulting is in all cases of congenital cyanosis the immediate cause of the symptomatology. The characteristic picture can be traced through the development of the compensatory mechanism of right heart hypertrophy and increased respiratory activity, and polycythemia, to the point where all these processes fail to supplement in the inefficient pulmonary circulation with oxygen sufficient for the body needs. The chronic asphyxia that develops is expressed, not only in the cyanotic hue of the patient, but also in the alterations at the periphery of clubbing and retinal changes. These are the direct results of delayed and toxic tissue metabolism,[1] and an overloaded systemic circulation.

The above considerations may be summarized by saying that the dependence of cyanosis, with its attendant phenomena, upon deficient oxygenation may be accepted as a fact; that the circulation is evidently able to accommodate itself to a certain degree of de-oxygenation, whether this be brought about by obstruction in the course of the pulmonary artery, by a general retardation of flow, or by a mingling of venous with arterial blood, but that as soon as deficient hematosis reaches a certain limit, oxygenation becomes insufficient for the needs of the body, and cyanosis results. Pulmonary obstruction alone appears capable of producing cyanosis, but it is still a question as to which of the above factors is the essential one, or in what degree they must be combined to bring the circulation to this limit, or what is the amount of venous blood which can circulate without producing symptoms of deficient aëration. That dilated peripheral capillaries, dark color and increased red cell content of the blood, must, when present, add their part to heighten the degree of discoloration is self-evident; but being themselves secondary, these conditions are not to be looked upon as etiological factors, but rather as concomitant effects of a common cause. Lastly, in complicated cardiac defects probably all the factors enumerated combine to produce the mulberry hue and the respiratory distress of the typical morbus cæruleus.

Symptoms.—The degree of discoloration varies from a slight bluish tinge of the cheeks and mucous membranes appearing on exertion or excitement, to a distinctly leaden hue of the whole surface, becoming purple in extreme cases. It usually increases gradually, and in many cases marked at the last it is absent at birth, appearing after weeks, months, or even years, when some intercurrent event has heightened the embarrassment in the pulmonary circulation. As a general rule, to which there are a good many exceptions, the degree of cyanosis may be said to depend upon the character of the defect. Thus it is usually *slight* or even entirely *absent, except during dyspnœic attacks,* or as a *terminal event,* in *patent foramen ovale, patent ductus,* or *septal defects;* a quite *moderate* degree characterizes those anomalies, such as *biloculate* or *triloculate heart,* in which there is a free intermingling of the two blood

[1] *Deut. Arch. f. klin. Med.,* 1910, xcix, 382.

streams, but no pulmonary obstruction; the *marked* cases such as are evident to every casual observer as "congenital heart disease," occur nearly always in *pulmonary stenosis* with or without septal defect; and the most *extreme grades*—the typical "blue baby," are seen in the complete interference with the blood supply to the lungs which takes place in *pulmonary atresia* or *transposition* of the great trunks.

The subject of advanced congenital cyanosis presents a striking appearance. The superficial vessels are often dilated, the face congested, the tongue "geographical," the eyes discolored, and sometimes bulging, the tips of the fingers, toes, and nose, flattened and bulbous, and the respirations heightened to actual dyspnœa. Traces of anasarca and œdema sometimes occur, but form no essential part of the picture, although of course present at the close in cases which terminate with failing compensation. The temperature is usually low, especially in the extremities, and there is a tendency to catarrh, severe coughs, and colds on slight provocation. Hemorrhages, especially from the nose, and spitting of blood are prone to occur. Disturbances of eyesight, dimness of vision or even blindness, may occur from neuroretinitis.

Delayed development is frequent. In Goodman's[1] case, patent ductus arteriosus in a boy aged fourteen, this was evidenced by retarded ossification of the pisiform bone of the wrist on *x*-ray examination (*Rotch's sign*). The patients are sometimes of very high intelligence, but when the cyanosis has set in early they are often stunted mentally as well as physically, somnolent in thought, and sluggish in action. In females the menstrual function is often delayed in onset, scanty, and irregular. In the cases with marked polycythemia, in addition to peripheral signs of venous congestion and plethora, cyclic (postural or orthostatic) albuminuria may occur. Parkes Weber records a case in a youth aged twenty-two, with great cyanosis and clubbing and a blood-count of 10,300,000 red cells, in whom repeated examination showed the early morning urine to be free from albumin, while that passed at 11 A.M., contained a considerable amount. Cyanotic patients bear the acute infections of childhood well, but frequently succumb to pulmonary tuberculosis. Another common cause of death is broncho-pneumonia.

Special Symptoms.—*Clubbing and Cyanosis Retinæ.*—These symptoms constitute the visible evidences of a generalized dilatation of the smaller bloodvessels over the body surface with accompanying productive changes. New formed capillaries, arterioles with thickened walls, tortuous dilated veins, and new connective tissue formation have been observed in advanced cyanosis, both in the skin (Variot and Gampert[2]) and in the lungs, as well as in the retina and bulbous finger ends. The causation of these vascular and tissue changes is certainly complex but their chief source is, undoubtedly, stasis and lack of oxygenated blood, and the effect that these conditions produce upon the tissues, by means of the toxic products of metabolism which escape oxygenation.

In *clubbing* of the extremities especially, these mechanotoxic factors are at work, and lead, in extreme cases, to what resembles a congestive

[1] *Amer. Jour. Med., Sc.*, 1911, xxiii, 509.
[2] *Gaz. d. Hôp.*, vol. xiii, p. 315.

type of scleroderma (Buhl). This is well shown in the cases reported by Ogle,[1] and by Groedel II[2] of a huge aneurism of the subclavian artery, which, by pressing upon and obliterating the axillary artery and vein and brachial plexus (Ogle's case), led to an enormous tumefaction with intense cyanosis and clubbing, strictly confined to the arm and fingers of the affected side.

Clubbing of pulmonary or hepatic origin, and that of chronic osteo-arthropathy (with proliferative changes in the shafts of the long bones), has been sharply distinguished from that of congenital cardiac disease on the ground that there is in the latter cases no new formation of bone (Ebstein[3]) and that the cause of the clubbing of pulmonary cases is absorption of toxins from the lung. Increased bone formation in the clubbed finger ends of the cardiac cases has been recorded, however, by Bamberger, Janeway,[4] Groedel II, and Miller.[5] Further, a case has been reported by Batty Shaw and Cooper[6] in which in the entire absence of pulmonary disease, signs of septal defect, with deep cyanosis, polycythemia and clubbing were combined with *thickening of the shafts of the tibia and other long bones* as well as of the clubbed terminal phalanges (*x*-ray examination). This indicates that in this case at least of congenital cyanosis we are dealing with a milder grade of one of the essential symptoms of Marie's disease.

The so-called hippocratic finger ends are broadened laterally and are slightly flattened, of bulbous appearance, with *distally curved nails*, (compare the more elongated finger ends and side to side convexity of the marked pulmonary cases). The nails are often shortened and without lunulæ and may be irregularly thickened from areas of vascularization or thrombotic processes in the matrix below. Microscopically, increase in the soft tissue and often in the fat (deficient aëration) is conspicuous; surprisingly little tissue change is sometimes manifest.

That direct admixture of venous blood is more important in the production of clubbing than pulmonary obstruction alone, is rather strikingly suggested by the fact that in our series, among 40 cases of pulmonary stenosis with open ventricular septum and closed foramen ovale, clubbing occurred in 20, while in 11 cases with closed ventricular septum and open foramen it occurred in 3; and in 7 cases of pulmonary stenosis with septum and foramen both closed, it was not present once.

Cyanosis Retinæ sive Oculi.—Cyanosis of the retina was described and figured in Liebreich's *Atlas*, in 1863. Eighteen published cases were collected by Posey[7] in 1905, and Holloway[8] has brought the number recorded to 27. Ocular changes would probably be found in nearly all cases of cyanosis if the eye grounds were examined, and this should always be done for diagnostic reasons; Babinski reported a case in which

[1] *Tr. Path. Soc.*, London, 1859, x, 103.
[2] *München. med. Wchnschr.*, 1906, liii, 264.
[3] *Deutsch. Arch. f. klin. Med.*, 1906, p. 66.
[4] *Amer. Jour. Med. Sci.*, 1903, cxxvi, 563.
[5] *Trans. Amer. Ped. Soc.*, 1904, xvi, p. 267.
[6] *Clin. Soc. Trans.*, 1907, vol. xl, p. 260.
[7] *Amer. Jour. Med. Sci.*, 1905, cxxx, 415.
[8] *New York Med. Jour.*, 1912, xiv, p. 71.

dilatation of retinal vessels preceded the appearance of cyanosis; so also Carpenter.

In this condition ophthalmoscopic examination reveals marked changes in the optic disk, congestive and secondarily inflammatory in character. The disk, itself, is unduly reddened or bluish, or sometimes hazy and swollen (neuroretinitis), and is traversed by numerous previously invisible capillaries, and by greatly broadened, often tortuous veins which sometimes show a deep reflex stripe along their surface, and are filled with dark brownish or even blackish-looking blood. The arteries may share in the dilatation and violet discoloration (as in 12 out of the 27 cases recorded), or they may be quite unchanged, showing up in sharp contrast; or again, as in the cases of Baquis and Stanglomeier, they may be contracted. Retinal hemorrhages are common. The difference in the appearance of arteries and veins was suggested by Nagel as diagnostic between anomalies due to admixture of currents (septal defects, etc.), and those due to pulmonary obstruction only, the arteries in the latter case remaining unaltered. This point has yet to be substantiated by postmortem evidence.

In advanced cases the ocular changes are not confined to the disk but involve the whole eye, which bulges outward (exophthalmos) and shows marked conjunctival congestion and cyanosis. Hemorrhages may occur into the vitreous or more superficially, and rupture of the cornea (Goldzieher[1]), or glaucoma, from congestion of the ciliary body, may occur. Severe iridocyclitis may develop, as in the cases of Goldzieher and Baquis.[2] In both of these the iris turned while under observation from a bright blue color to a yellowish brown, a change found by the ocular microscope to be due to extreme congestion. This symptom was the more remarkable because it was seen to disappear after death. Baquis' case was a boy aged eleven, with extreme cyanosis and clubbing, a blood count of 8,500,000 red cells and pulmonary stenosis with septal defect. He gives a careful description of the microscopic findings in the diseased eyeballs and adds a study of eight other cases in the German literature.

Dyspnœa.—Investigation into the respiration of cyanotic cases has been carried out by special methods of precision by Rubow,[3] and Bie and Maar.[4] They show that neither total nor vital capacity is increased, probably because of the hypertrophied heart and dilated veins which commonly occupy so large a part of the thorax, but that the essential compensatory change consists of an increased pulmonary ventilation, by acceleration of the respiratory rate. Dyspnœa is the response made by the centre in the medulla to irritation by the unaërated blood. Peabody[5] regards it as due to increased acidosis with increased excitability of the respiratory centre. It is a prompt and early feature. It usually sets in before the cyanotic color is manifest. It frequently culminates in the so-called *dyspnœic attacks*, which in their typical form and full develop-

[1] *Centralb. f. prak. Heilkunde*, September, 1904.
[2] *von Graef's Arch. f. Ophth.*, 1908, lxi, 68.
[3] *Deut. Arch. f. klin. Med.*, 1908, xcii, 255.
[4] *Ibid.*, 1910, xcix, 382.
[5] *Arch. Int. Med.*, 1914, xiv, 236.

ment, are seizures of extreme respiratory distress usually attended by marked cyanosis, and sometimes by unconsciousness, in which death may take place. Such attacks are characteristic of all severe cases of cyanosis but are frequent also in such conditions as patent ductus arteriosus in which there may be no trace of cyanosis except at these times. Transient cyanosis of this type has been described by Sebilleau[1] as La Cyanose Paroxystique Congénitale. Respiratory failure may be evidenced also by repeated syncopes or by anginal crises.

Polycythemia.—This is now well recognized to be a common characteristic of cyanotic blood. The red cells frequently number 7,500,000 to 8,500,000, per cmm. the percentage of hemoglobin is raised, and in some cases the red cells are also increased in size. Counts of 12,750,000 are reported by Murray Leslie,[2] 10,000,000 by Pick and Parkes Weber, and 9,000,000 by Vaquez and Quiserne.[3] Bernstein[4] reports a case of congenital cyanosis coming on at the sixteenth month, with death at two and one-half years, in which the red cells numbered 10,000,000; the tricuspid orifice was absent and the right heart aplastic with defective interauricular and interventricular septa.

The increase of the red cells is generally thought to be of the nature of a compensatory process, and has been compared to the polycythemia of high altitudes. Weil describes in detail a microscopic finding in two cyanotic children with pulmonary stenosis in whom the red cells numbered respectively 7,502,000 and 8,540,000. The hematopoietic organs and also the other tissues examined were crowded with vasoformative cells and embryonic capillaries and the bone marrow showed a typical erythroblastic reaction. Similar appearances have been noted by other observers and prove that this feature is part of the compensatory mechanism of the organism for the better oxygenation of the tissues.

The blood count differs somewhat at different parts of the body and according to whether the specimen has been drawn from arteries, veins, or capillaries but it remains far above the normal, the increase in red cells remaining an absolute and not a relative quantity (Bie and Maar). That is to say in these cases the total quantity of blood in the vessels is increased, a moderate degree of hydremia existing.

Polycythemia is not a constant feature in congenital cyanosis, it is characteristic rather of the later stages of the disease, and while favorable in so far as it represents an attempt at compensation, its appearance points to a grave prognosis.

Diagnosis.—The cyanosis of congenital cardiac disease must be differentiated from a number of other forms. Of first importance among these is the so-called enterogenous cyanosis[5] (first described by Stockvis and other Dutch observers), in which the dark color of the blood is due to a

[1] *Thèse de Paris*, 1895. [2] *Proc. Royal Soc.*, Clinical Section, 1908, i, 34.
[3] *Compte rendu de la Soc. de biol.*, July 10, 1904.
[4] *Ibid.*, 1902, p. 915.
[5] A digest of enterogenous cyanosis, with a tabulated statement of the recorded cases and full bibliography, is given by West and Clarke (*Lancet*, February 2, 1907). Other important articles are by Hymans van der Bergh (*Deutsch. Archiv f. klin. Med.*, 1905), Oliver (*Lancet*, December 29, 1906), Gibson (*Lancet*, July 14, 1906), and Blackader (*New York Med. Jour.*, March 16, 1907, lxxxv).

sulph-hemoglobinemia or methemoglobinemia, produced, it is thought, by the action of hydrogen sulphide or other toxic agents upon the blood. Again, certain aniline poisons lead to a methemoglobinemia giving a dark discoloration to the skin, and polycythemia with splenomegaly is sometimes, although not always, associated with cyanosis. These conditions differ from congenital cyanosis in the slightly different tinge of the skin, which in methemoglobinemia is of a grayish hue, in polycythemia with splenomegaly of a more florid aspect, by the absence of cardiac signs, by the presence of intestinal symptoms, and by the history of a toxic factor or the presence of enlargement in spleen and liver. In methemoglobinemia the red cells are not increased in number. Other conditions leading to cyanosis with clubbing are pulmonary emphysema, bronchiectasis, and adherent pericardium.

CLASSIFICATION.

Many attempts have been made to reduce cardiac anomalies to a scientific classification, but none have been entirely successful. The most logical arrangement is undoubtedly one based upon the stage of development at which the defect has occurred, differentiating those cases due to arrest of growth from those originating at a period of intrauterine life and apparently caused by fetal disease. Our knowledge of the development of the heart is still too limited to permit of a complete classification on this basis, and, on the other hand, the etiology of a given condition is often impossible to decide in the individual case. Moreover, a grouping based on development alone is sometimes unpractical, for widely different pathological results may ensue from arrest of different parts of the heart at about the same period of fetal life. For these reasons no one classification will be found adequate in its practical application, and it would almost seem that a grouping "on mixed principles" is the only one under which all the cases can be satisfactorily placed.

The 631 cardiac defects here studied present, either as the primary lesion or as a complicating condition, illustrations of practically all the cardiac anomalies known. In the tables[1] of relative frequency, age, sex, etc., pages 342 and 343, an attempt is made to arrange these cases in as logical an order as possible. It represents an attempt at a detailed classification based on strictly anatomical principles and on development so far as this is known, but without regard to the etiology, which is so often obscure. Thus the group of stenosis and atresias of valvular orifices is subdivided, not into inflammatory and developmental forms and their subdivisions, with or without transposition or *rechtslage* (Rauchfuss, Vierordt), but on anatomical considerations only, with regard to the seat of the stenosis and the presence or absence of septal defects.

[1] NOTE.—"Double" indicates a systolic with a diastolic murmur. The sex is not always mentioned in the records of cases. The numbers in these columns do not, therefore, always correspond to the totals in the chart. The data given as to age, sex, postmortem findings, and clinical aspects refer to the cases in the first column in the chart. This column is repeated in the third to last column, and this, added to the second to last column, gives the total relative frequency of each defect, whether classified as primary lesion or as complicating other defects.

Statistics of Congenital Cardiac Disease (631 Cases Analyzed).

| Classification of Defect. | Number of cases analyzed. | Age. Maximum. | Age. Minimum. | Age. Mean. | Sex. Male. | Sex. Female. | Postmortem Findings. Cardio-vascular system. Fetal passages. Patent D. A. | Fetal passages. Defect A. S. | Fetal passages. Defect V. S. | P. A. Dilatation. | P. A. Hypoplasia. | Aorta. Dilatation. | Aorta. Hypoplasia. | Rechtslage of aorta. | Collateral circulation. | Arterial disease. | Acq. valv. dis'se. Acute endocarditis. | Acq. valv. dis'se. Chronic lesion. | Hypertrophy of heart. R. auricle. | Hypertrophy of heart. R. ventricle. | Hypertrophy of heart. L. auricle. | Hypertrophy of heart. L. ventricle. | Assoc. anomal. In heart. | Assoc. anomal. In vessels. | Assoc. anomal. Elsewhere. | Clinical. History. Personal. Hereditary predisposition. | Rheumatism. | Tuberculosis. | Congenital syphilis. | Infectious dis. recovry | Special symptoms. Cyanosis. Slight. | Moderate. | Marked. | Terminal. | Clubbing. | This feature not analyzed. | Cyanosis retinæ. | Dyspnœa | Dyspneic attacks. | Delayed development. | Physical signs. Cardiac. Vascular. | Precordial bulging. | Pulsation. | Thrill. | Dulness above +. | Second pul. sound +. | Murmurs. Presystolic. | Systolic. | Diastolic. | Double. | Continuous. | Causes of death. Defect. Sudden. | Failing compensation. | Bronchopneumonia. | Cerebral disease. | Infectious disease. | Relative Frequency. Number classified as primary lesion. | Number complicating other defects. | Total incidence. |
|---|---|---

| | | |

The majority of cardiac defects are complicated, and it is often difficult, sometimes impossible, to say which is the primary lesion; many of the cases present other anomalies of equal importance with those with which they are grouped. A cross-index has therefore been made in the two columns next to the end, and the total relative frequency is to be found in the last column of the chart.

ANOMALIES OF THE PERICARDIUM.

Absence or Defect.—The Pericardium may be entirely *absent*, as in some forms of ectopia cordis, or its parietal layer may be more or less *defective*. Some forty-two cases are on record and the subject has recently been reviewed by Ebstein,[1] Plaut,[2] McGarry,[3] and Cameron. The defect always involves the *left* side of the sac but it may vary from a localized hole with smooth edges lying over the pulmonary artery opposite the root of the left lung and communicating with the left pleura, to complete absence of the parietal layer, the heart lying in the anterior mediastinum, without any serous envelope. In all the cases recorded except the four above mentioned, the whole left and anterior walls of the pericardium are wanting, and the heart and left lung lie in a common cavity, the left pleura being continuous with the epicardium and the anterior and right walls of the sac being represented by one or more rudimentary folds; in the best developed cases two folds, one sagittal and one crescentic; spring from the diaphragm and are inserted, the one into the anterior mediastinum and the other posteriorly at or near the root of the left lung; in the more extreme cases the diaphragm is free and a serous fold encircles the base of the heart with the great trunks; in complete defects no trace of the parietal layer may exist, or it may be represented by a few fatty appendices arranged fringe-like about the base of the heart. The left phrenic nerve maintains its relationship to the pleuropericardial septum, running down parallel to the border of the sagittal rudimentary fold when this is present, and is displaced to the right in a degree increasing with the degree of the defect. This anomaly in the course of the nerve, and the serous investment of the margins of the defect, are points diagnostic of its congenital origin.

Pathogenesis.—An explanation of the condition is to be sought toward the end of the fifth week of fetal life, when the pericardial begins to be separated from the pleural cœlom. At this time the so-called pulmonary ridge, an elevation from the walls of the ducts of Cuvier, encircles, and gradually obliterates, the canal of communication between the two cavities, and descends to the septum transversum or primitive diaphragm as the pleuropericardial septum. Under normal conditions the left duct of Cuvier atrophies in early fetal life. Pericardial defect, with its invariable relation to the left pleural cavity, may well be due, as suggested by Perna, to a too early atrophy of this structure, dependent upon some anomaly of circulation in the great venous trunks, the arrested develop-

[1] *München. med. Wchnschr.*, 1910, lvii, 522.
[2] *Frankf. Zeitsch. f. Path.*, 1913, xii, 141.
[3] *Anat. Record*, 1914, February 20.
[4] Trans. Chicago Path. Soc., 1914, ix, p. 148.

ment of the pulmonary ridge resulting leading to a localized defect (pleuropericardial foramen), or to the more or less complete absence of the pleuropericardial septum. In one of Keith's cases, a defect of the left pleuroperitoneal membrane is also to be concluded, for the heart, left lung, liver, spleen, and stomach lay in the left pleuropericardial cavity.

Clinical Aspects.—The defect in itself has no direct effect upon the heart, the patients reaching adult life, and sometimes even attaining advanced age without any untoward sign. Its *clinical significance* depends chiefly upon two factors: First of these is the abnormal juxtaposition of the heart and left lung, whereby the heart is exposed, without the protection of its serous envelope, to the many inflammatory changes prone to attack the pleura; some cause also, whether traction from adhesions with the constantly pulsating heart or friction with the surface of this, appears to act deleteriously upon the left lung and pleura, predisposing these to disease. Among the forty cases recorded the incidence of left-sided pulmonary complications is extremely large. Picchi's two patients died of left lobar pneumonia, Weisbach's of left purulent pleurisy, Powell's of left pneumothorax, Plaut's second case and Faber's of acute left-sided pleurisy and Baly's, Hughes', and Saxer's of pulmonary tuberculosis.

Secondly, the *cor mobile* resulting from the lack of pericardial attachment to the diaphragm and mediastinal structures, may lead to sudden kinking of the great vessels resulting not only in symptoms of precordial distress (Ebstein), but apparently, in one instance at least in death itself. In the case recorded by Boxall death occurred on the third day after confinement, apparently from the sudden slipping of the heart's apex out of a low-walled pouch formed by two rudimentary folds attached to the diaphragm, in the altered intrathoracic pressure following delivery. Thirty hours before death urgent dyspnœa, collapse, and a systolic murmur over the precordium suddenly appeared. Pulmonary thrombosis was suspected, but was not confirmed at autopsy, when the heart was found in the left pleura. The number of fatalities is high.

Diagnosis.—This is difficult, but does not seem impossible. The greatly increased mobility of the heart, its occasional hypertrophy either from this cause or from the traction of inflammatory fibrous tissue bands attaching it to the left pleura and diaphragm, and its frequent displacement to the left through such traction or from similar causes are the chief points. In spite of its rarity, pericardial defect should always be considered in the light of the *x*-ray findings.

In Faber's case, a man of fifty-one years, in good health until five weeks before death, when an extensive left pleural effusion developed, the heart was only moderately displaced to the right before aspiration, although the left chest was entirely dull; after the withdrawal of 2200 cc. of fluid the apex was evident in the third and fourth interspaces in the left anterior axillary line, and at a later aspiration of 3100 cc., the heart was felt in this region by the aspirating trocar. These facts supplied a basis for a correct diagnosis.

Unattached Pericardium.—Turner describes an adult male subject in whom the parietal pericardium was perfectly free from continuity

with the central tendon of the diaphragm or other structure, and was attached only about the base of the great vessels, closely embracing the heart, which could be drawn completely out of the chest (*cor mobile*), the inferior vena cava lay free in the thorax for an inch before piercing the pericardium. A similar condition was observed in the walrus and was thought here to be normal.

Diverticulum or Hernia Pericardii.—This consists in a localized bulging of the serous, or serous and fibrous, coats of the parietal layer, whereby a thin-walled cyst is formed, communicating with the pericardial cavity either directly by a narrow orifice, or by a tubular canal. An interesting example was seen by the writer in the Museum at Bologna, from a case published by Coen.[1] In this specimen a unilocular chamber of a capacity of 40 cc., formed by the protrusion of the serosa, projected from the right border of the parietal pericardium, as a kidney shaped tumor 17.5 cm. in circumference, and communicated with the interior of the pericardial sac by a minute orifice lying at the bottom of a small fossa. Coen gives an analysis of ten other cases in the literature.

This condition is of little clinical importance, usually remaining latent. Secondary pathological changes, such as calcification or fibrosis of the cyst walls, or occlusion of its orifice and consequent distension of its cavity may supervene, and make it an impediment to the heart's action. The possibility of a pericardial diverticulum should not be overlooked in the diagnosis of mediastinal tumors.

DISPLACEMENTS OF THE HEART.

Ectopia Cordis.—By this term is understood a displacement so that the heart passes out of the thorax, and comes to lie either upon the outer surface of the body or in the abdominal cavity. Full bibliographical studies, with reports of cases, are given by Jones,[2] and by Ellis.[3] The latter, following Rauchfuss, recognizes three forms, (1) *cervical* heart, in which the organ lies high up in the neck; (2) *pectoral* heart with fissure of the sternum, and (3) *abdominal* heart in which the heart is projected through a defect in the diaphragm into the abdominal cavity.

The existence of cervical heart, or of pectoral heart with fissure of the upper part of the sternum and absence of pericardium, is not compatible with life; in abdominal heart on the other hand life is not necessarily shortened (witness Deschamps' case of a healthy soldier whose heart occupied the position of the left kidney in the lumbar region), and in pectoral heart with inferior sternal fissure and pericardium present, it might with due care be indefinitely prolonged. In Goode's[4] patient, with fissure of the sternum below the manubrium, the heart was oiled every three hours and kept covered by a cardboard box, and the child did very well for a time. Ellis quotes a case in which a thin membrane covering the heart sloughed on the fifteenth day, and the outer skin

[1] *Bull. della Soc. Med. Chi. di Bologna*, 1885, xv, Fasc. 1.
[2] *Trans. Path. Soc.*, London, 1869, xx.
[3] *Proc. Path. Soc.*, Philadelphia, 1906, p. 36.
[4] *Virginia Med. Semi-Monthly*, 1904, p. 555.

covering the organ was successfully united by sutures. He suggests that such operative interference might be tried in suitable cases where the visceral pericardium is present.

Dextrocardia.—This term is applied clinically to all cases in which the heart is found displaced to the right side of the thorax. Pathologically two conditions must be distinguished. In the one the heart is simply displaced to the right as a result, usually, of acquired disease (*Dextroversio cordis*). In the other the organ is also more or less altered in its position in the thorax, so that *the apex comes to point to the right.* In these latter cases two forms must again be recognized:

A. The heart is not transposed, but appears to have undergone a simple rotation from left to right on its vertical axis, so that its left chambers come to lie more anteriorly and its right chambers more posteriorly. The apex points to the right but is formed not of the left but of the right (venous) ventricle, which remains on the right side and receives blood from the right (venous) auricle into which the venæ cavæ empty. This, which is not a true transposition, is the condition present in the majority of the cases of congenital dextrocardia. It is well illustrated by Grunmach's[1] case (See Fig. 21.)

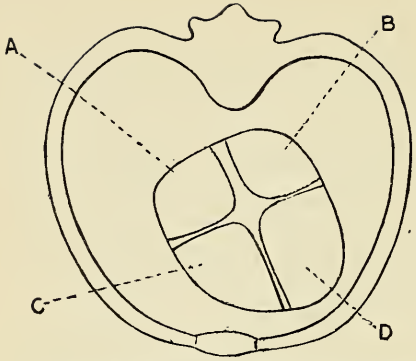
B. The heart may be completely reversed upon itself, those parts normally upon the left coming to lie on the right side, but the relation of the various structures to each other remaining unchanged, so that a complete mirror picture of the normal heart results. Here the apex, pointing to the right, is formed of what was normally the left ventricle, which now lies on the right side and communicates with the right (normally left) auricle which receives the pulmonary veins and is structurally the systemic auricle. In complete situs inversus this "mirror" condition is the rule, but true transposition of the heart only, without situs inversus is exceedingly rare, the only cases we know of on record being these of Graanboom[2] and Rokitansky.

The etiology of these two types of congenital dextrocardia differs widely. Nagel[3] reviews six cases with clinical and autopsy reports in the literature, and demonstrates, with the aid of diagrams, that five of these, namely, those by Grunmach, Geipel, Löwenthal, Barmwerth and himself, belong to the type A above, in which the heart is not transposed, but presents simply a persistence of the embryonic stage, in which the apex was formed by the right half of the common ventricle. The fact that in all five of these cases the grave anomalies of pulmonary stenosis and ventricular septal defect were associated, affords convincing proof that a primary arrest of development had occurred.

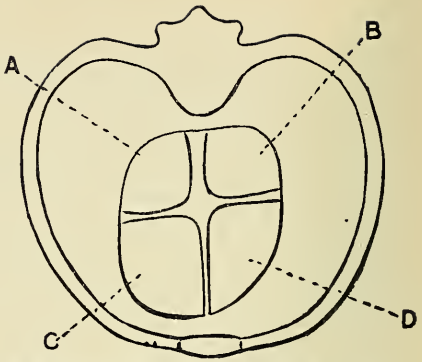
In the sixth case, on the other hand, that by Graanboom, in which there was true transposition of the heart, and the septum was entire, the probable explanation is to be sought, not in an arrest of development, but, with the causes of transposition in general, in the altered relation of the embryo to the primitive chorionic villi.

Congenital dextrocardia, unassociated with other anomaly, is not

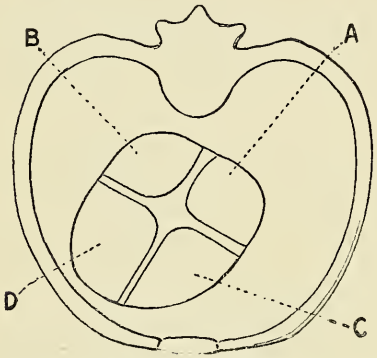
[1] *Berlin. klin. Wchnschr.*, 1890, No. 2.
[2] *Zeitschr. f. klin. Med.*, 1891, Bd. 18, 2.
[3] *Deut. Arch. f. klin. Med.*, vol. xcvi, p. 552.



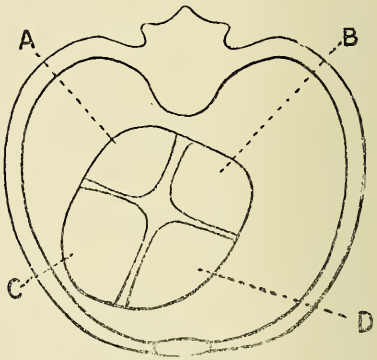
1. Normal heart. *A*, caval auricle; *B*, pulmonary veins auricle; *C*, right ventricle (caval blood ventricle); *D*, left ventricle (pulmonary blood ventricle).



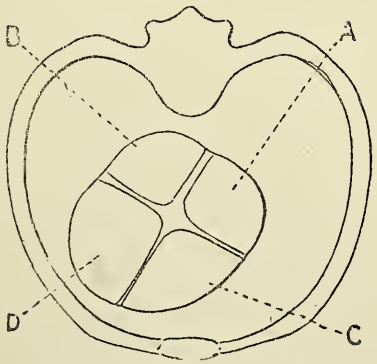
2. Embryonic heart. *A*, caval auricle; *B*, pulmonary veins auricle; *C*, right ventricle (caval blood ventricle); *D*, left ventricle (pulmonary blood ventricle).



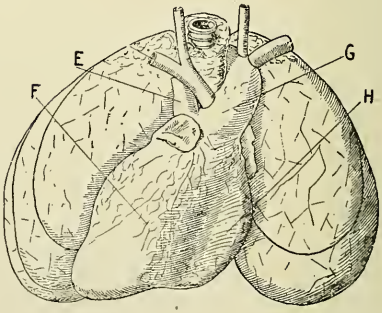
3. Mirror picture of normal heart. *A*, caval auricle; *B*, pulmonary veins auricle; *C*, right ventricle (caval blood ventricle); *D*, left ventricle (pulmonary blood ventricle).



4. Pure congenital dextrocardia. *A*, caval auricle; *B*, pulmonary veins auricle; *C*, caval blood ventricle; *D*, pulmonary blood ventricle. Note similarity to No. 2.



5. Graanboom's case of congenital dextrocardia (mirror picture). *A*, caval auricle; *B*, pulmonary blood auricle; *C*, caval blood ventricle; *D*, pulmonary blood ventricle.

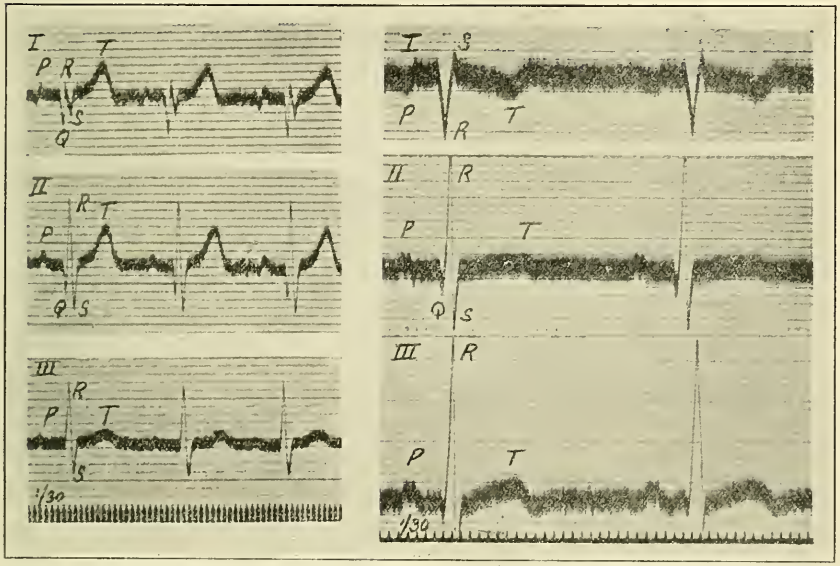


6. Grunmach's case of pure congenital dextrocardia (arrest in embryonic stage). *E*, vena cava superior; *F*, ventriculum dextrum; *G*, aorta; *H*, ventriculum sinistrum.

1, 2, 3, 4. Diagrams (1) showing normal heart; (2) embryonic heart; (3) mirror picture of normal heart; (4) heart in usual type of pure congenital dextrocardia; (5) from Graanboom's case of pure dextrocardia (mirror picture). Note that the apex is formed by the left (pulmonary blood) ventricle. (From Nagel's article on Pure Congenital Dextrocardia in the *Deutsches Archiv. f. klin. Med.*, xcvi, p. 572.) (6) Grunmach's case of pure congenital dextrocardia; arrest of development, persistent embryonic stage. Note that the apex is formed by the right (caval blood) ventricle. (From his article in the *Berl. klin. Wchnschr.*, 1890, page 22.) The auricles are designated "caval" and "pulmonary" (according to the veins they receive), instead of right and left, in order to show the difference in situation in the mirror picture and in Graanboom's case, from that of the usual type of pure congenital dextrocardia (Grunmach's case).

itself of clinical significance and may be discovered accidentally with the heterotaxy that usually accompanies it, in a perfectly healthy subject, by physical and *x*-ray examination, which reveals the normal area of cardiac dulness on the right side, with corresponding location of sounds and fluoroscopic findings. Transposition of the heart, of the type usually associated with situs inversus viscerum (Graanboom's case) yields a characteristic electrocardiogram (Neuhof,[1] Lewis[2]), in that Lead I, shows a reversal of all curves, and Leads II and III, replace each other. This supplies a diagnostic point between the transposed and non-transposed forms of Congenital Dextrocardia and also distinguishes the former from a dextroversio, in which the electrocardiogram, although atypical, is not reversed. The curves in this latter condition have been studied by Neumann.[3]

FIG. 22



1. Electrocardiogram from a case of congenital dextrocardia with transposed (mirror-picture) heart. Note that: Lead *I*, is completely reversed in that *P*, *R*, and *T*, normally directed upward in this lead, here point downward. Lead *II*, has changed places with Lead *III*.

2. Electrocardiogram from a case of dextro-versio-cordis, *i. e.*, simple displacement of the heart to the right. Here there is no reversal of leads, but Lead *I* especially deviates from the normal in *Q* and *R*. (From Clinical Electrocardiography, by Thomas Lewis, London, 1913.)

Incomplete Heterotaxy.—Of interest are three cases reported by Hickman, Royer and Wilson,[4] and McCrae, of transposition of the viscera with only partial transposition of the heart, which maintained its normal position with *apex pointing to the left*, the ventricles and auriculo-ventricular ostia unchanged, but the auricles and great arterial trunks transposed, and the auricular septum defective. In McCrae's and

[1] *Jour. Amer. Med. Assn.*, 1913, lx, p. 1064.
[2] *Clinical Electrocardiography*, 1913, p. 100.
[3] *Deutsch. med. Wchnschr.*, 1912, xxxviii, p. 1920.
[4] *Arch. Pediat.*, 1908, xxv, 882.

Hickman's cases the pulmonary artery was atresic, in that by Royer and Wilson it was stenosed, and arose from the right ventricle with the aorta but in transposed relation. The ventricular septum was entire in McCrae's case, defective in the other two.

Intrinsic Displacement of Chambers.—Four interesting examples, in anencephaly and ectopia cordis, of displacement of the chambers upon each other, as a result of extraneous mechanical force exerted on the heart after it was fully formed, are reported by Jane Robertson.[1]

ANOMALIES OF THE HEART AS A WHOLE.

Acardia, Hemicardia.—Where grave interference with the circulation occurs at a very early embryonic period, the heart may not develop at all (acardia), or it may be rudimentary (hemicardia). Such a condition usually develops in one member of a uniovular twin pregnancy in which anastomosis of the vessels of the two individuals can take place through their common placenta.

All degrees of acardia may occur and from the developmental standpoint the findings are extremely interesting. Thus Campbell and Shepherd report a case in which the circulation had been interfered with before the heart had formed at all, and in which the two dorsal arteries passing from the umbilical opening toward the head of the amorphous monster, represented a persistence of the early vitelline circulation. Kehrer[2] adds to an analysis of thirteen cases from the literature an account of a case of his own which is remarkable for the advanced state of the rudimentary organ. Cases not included in Kehrer's review are reported by Schubert[3] and by Näcke and Benda.[4]

Multiple Hearts.—This phenomenon is commoner in animals. An explanation is perhaps to be sought in an irregular division of the omphalomesenteric or vitelline veins, from which the first heart *anlage* is derived.

Bifid Apex.—This may occur without other anomaly or complicating grave defects. The apex of the early embryonic heart during its amphibian stage, is bifid; a condition to be ascribed to the rapid downward growth of the apices of both ventricles at this time, so that a deep interventricular groove or cleft is formed. Obliteration of this cleft takes place in embryos over 11 mm. long, by the development downward of the embryonic apex, which occurs simultaneously with the closure of the interventricular foramen. In the adult mammalian heart bifid apex is thus to be ascribed to a persistence of the interventricular groove (Gegenbaur), due to an arrest of development of the embryonic apex, as is evidenced by the absence of the muscular vortex normally present here, each apex in the bifid state being formed independently from musculature derived respectively from the musculospiral and sinospiral bands (Mall).[5] A deeply bifid apex is normal in the dugong; it occurs in 3 of Thérémin's 106 cases and in 15 of our series.

[1] *Jour. Path. and Bact.*, 1913, xviii, 211.
[2] *Arch. f. Gynäk.*, 1908, lxxxv, 121.
[3] *Monatsch. f. Geburts.*, 1908, xxviii, 3.
[4] *Zentralbl. f. Gynäk.*, 1907, p. 17.
[5] *Anat. Rec.*, 1912, vi, 167.

Diverticulum.—The heart may be prolonged into a hollow process. Arnold[1] reports a female child, aged two and a half months, a subject of congenital lues, in whom the apex of the left ventricle ran out into a hollow process which bent around like a hook, its blind end projecting upward and to the left. In Koller-Aeby's[2] case it formed a pulsating process with muscular walls descending from the apex of the left ventricle through a defect in the diaphragm to form part of an umbilical hernia. Diverticulum of the heart is rare and of no clinical significance.

Primary Congenital Hypertrophy.—Recently a number of observations have been published in which hypertrophy of the heart existed at birth. In 1898, Simmonds[3] reported the first clear case of primary congenital hypertrophy. In a newly born child which died during a protracted labor all the organs including the kidney were normal, but the heart was greatly enlarged. It weighed 44 gm. (normal weight 19 to 20 gm.); the right ventricle was 0.75 to 1 cm., the left 1 to 1.25 cm. thick. The papillary muscules were small and took no part in the hypertrophy, thus indicating that this was not caused by overwork. Simmonds suggests that the hypertrophy may have been due either to some cause in early embryonic life, which may later pass away, or to Virchow's diffuse myomatous infiltration. Other typical cases of congenital hypertrophy without valvular disease, nephritis, or apparent cause, are reported by Effron,[4] Kalb,[5] and Ratner.[6]

Congenital Rhabdomyoma.—An interesting problem is presented by the occurrence in infants or young children of embryonic muscle tumors of the heart wall associated, in the majority of the cases, with sclerosis of the cerebral cortex. The condition was first described by von Recklinghausen and by Virchow and was first reported on this Continent by Knox and Schorer.[7] Wohlbach[8] has recently studied the 11 cases on record, and has added an observation of his own of an instance in which a rhabdomyoma of the wall of the right ventricle was associated with multiple nests of neuroglia in the spinal meninges. The child, a female, with hydrocephalus and spina bifida and paralysis of the lower half of the body from birth, died of scorbutus at ten months. The heart was very large, weighing 72.5 gm., with hypertrophied papillary muscles. Just below the pulmonary valve an ovoid nodule, 1.7 x 4 cm. wide, of grayish-red color and elastic consistence, lay imbedded in the interventricular septum and in the papillary muscle of the anterior tricuspid valve segment, to which it supplied chordæ. Microscopically it was composed of a delicate reticulum of connective tissue supporting heterogeneous cells having a more or less irregularly striated fibrillary matrix and containing in many instances large intracellular spaces and peripherally placed nuclei, the whole bearing a *bizarre* resemblance to the modified muscle cells (Purkinje fibres) of the adult heart.

An explanation of this remarkable combination of congenital cerebral

[1] *Virchows Arch.*, 1894, cxxxvii, 318.
[2] *Arch. f. Gynäk.*, 1907, lxxxii, 185.
[3] *München. med. Wchnschr.*, 1898.
[4] *Zurich Thesis*, 1903.
[5] *Munich Thesis*, 1906.
[6] *Berlin Thesis*, 1912.
[7] *Arch. Pediat.*, 1906. xxiii, 361.
[8] *Jour. Med. Research.*, 1907, xvi, 495.

sclerosis with rhabdomyoma may be sought in the fetal malnutrition invariably present, which may have led to the vascular degeneration that must underlie such changes (Wohlbach).

ANOMALOUS SEPTA.

Anomalous cords, bands, or septa may arise within the heart, and lead, when sufficiently pronounced, to a division of the chambers, and the so-called double or supernumerary cavities.

Anomalous Septa in the Left Auricle (Double Left Auricle).—Of this interesting condition there are eight fully reported cases, by Church (1868), Fowler, Martin, Griffith (2 cases), Potter and Ransom, Borst, and Hosch,[1] all of which are summarized in an article by the latter writer. In these cases, a membranous diaphragm perforated by one or more openings stretches across the left auricle, dividing it into a right postero-superior chamber, which receives the pulmonary veins and contains the interauricular septum, and a left antero-inferior chamber, in which lies the auricular appendix and the mitral orifice. The blood from the pulmonary veins enters the large upper chamber and passes thence through the small opening in the diaphragm into the lower chamber to the mitral orifice. When the foramen ovale is patent, a large portion of the pulmonary blood may pass through the open foramen into the right auricle, thus depleting the greater circulation and throwing the bulk of the work on the right heart, which, as in this case, becomes greatly hypertrophied, and the left chambers very small.

Borst gives a careful anatomical study of his case, which throws much light on the etiology. In a woman, aged thirty-eight years, dying with failing compensation, the heart was of a quadrate shape, the right ventricle much hypertrophied and dilated, the left auricle also greatly dilated. There was no communication between the auricles, but the valvula formanis ovalis was absent. The left auricle was divided into a large upper cavity receiving the pulmonary veins and a small lower chamber containing the mitral orifice by a diaphragm which ran from above anteriorly and externally, downward, inward and backward. This diaphragm presented at its insertion below and behind, a round hole, 1 cm. across, which was the only communication between the two cavities through which the blood from the pulmonary veins could be transmitted to the mitral orifice.

Borst explained this anomalous diaphragm as the malposed *septum primum* which had been deflected to the left in the embryonic heart by a displacement of the pulmonary veins to the right, so that they entered the auricles between the *septum primum* and *secundum*, and had thus formed between them this large secondary cavity. The hole in this anomalous septum, which communicated with the smaller cavity below, he looks upon as the *ostium secundum* (patent foramen ovale).

Borst's explanation receives corroboration in a remarkable way from what may be termed a complementary case reported by Sternberg[2]

[1] *Frankf. Zeitsch. f. Path.*, 1907, i, 56.
[2] *Verh. der XVI Deut. path. Gesell.*, 1913, p. 256.

in which three auricular chambers were present, separated from each other by strong septa. The left chamber received the pulmonary veins and contained the mitral orifice, and communicated with the middle chamber by a large ovoid foramen (the ostium primum of Born), situated in the lower portion of the anomalous septum (S. primum) just above the mitral valve. This middle chamber received the superior cava only and communicated with the remainder of the right auricle, which received the inferior cava, by a large opening. Sternberg explained the formation of the middle chamber by a displacement to the *right* of the septum secundum, due to a malposition of the inferior cava, which entered too far to the *left*, and pushed the septum secundum to the *right*, just as in Borst's case the anomaly was due to the entrance of the pulmonary veins too far to the *right*, so that they cut off a middle chamber by pushing the septum primum to the *left*.

An *anomalous* band several cm. long and as thick as a knitting needle may traverse the left auricle. Cases were recorded by Browicz, Rolleston and Hosch.

Anomalous Septa in the Right Auricle.—These are quite different both in structure and origin from those in the left auricle. The condition was first described and figured by Chiari,[1] on the basis of 11 original cases. In all these a system of fine cords, or a reticulum of delicate tissue identical in structure with the Eustachian valve and attached to this or to the Thebesian valve stretched across the auricle to be attached to the crista terminalis or auricular septum or other points. Similar structures in the right auricle have been recorded, and are to be ascribed, as Chiari pointed out, to a persistence and anomalous development of the *septum spurium* or of the right and left valvulæ venosæ. These are the lips of the opening of the embryonic sinus venosus into the right auricle. In normal development they become merged with the Eustachian and Thebesian valves, and with the septum secundum. In a case by Lesieur and Froment[2] of a gaping foramen ovale with an anomalous valve of Thebesius, 6 cm. high, which projected as a fenestrated, incompletely attached, shelf across the right auricle, these authors ascribe both anomalies to the maldevelopment of the *valvula venosa sinistra*, which failed to close in the foramen ovale by merging with the septum secundum. A connection between these two anomalies is further established in Ebbinghaus's case, in which Chiari's fenestrated network extended across the auricle from the Eustachian valve, and the interauricular septum showed fifteen small and two large perforations. Persistent left superior cava is also frequently associated.

Clinical Aspects. When uncomplicated by other defects, such septa may exist without giving any evidence of their presence. All the cases of double left auricle recorded were in adults, except that by Hosch. There are certain dangers, however. When the septum is strongly developed, it is liable to hamper the blood stream. Church's case, and Borst's, both died at thirty-nine years of failing compensation, and Borst's patient suffered from earliest youth from dyspnœa. Again the fine

[1] *Ziegler's Beitr.*, 1897, xxii., 1.

[2] *Lyon Médical*, 1911, xcvi, 1045.

reticulum that occurs in the right auricle may supply a possible nidus for thrombotic processes, which may lead to pulmonary embolism and death. This happened in Chiari's first case, and thrombosis is related also by Thilo and Thorel.

Anomalous Septa in the Ventricles.—These again have a very different origin from those in the auricles. The commonest form is a septum shutting off the conus from the sinus of the right ventricle, which probably represents arrest at an early stage in the development of the heart, explained by Keith as a "persistence of the lower bulbar orifice." Such septa have usually undergone much fibrous thickening, and have been ascribed by many observers to inflammatory contraction, but in a case reported by Bohm all evidence of fibrosis was absent, and the conus was separated from the sinus by a simple muscular ridge. Two cases reported by Stephen Mackenzie[1] of hearts showing "three ventricles," separated by incomplete septa, probably belong here.

In another type of anomalous septum, a rudimentary chamber giving off the pulmonary artery, or the (transposed) aorta is cut off from a common ventricle which receives both auriculoventricular orifices, by what appears to be the malposed and defective interventricular septum. This type is well illustrated by the Holmes specimen in the McGill Museum (described and figured under Triloculate Heart, page 373). There are eight similar cases in the literature, but in all except that of Holmes the aorta and pulmonary artery were transposed.

Anomalous chordæ tendineæ frequently cross the ventricles at irregular points. They may consist of fibrous tissue with or without ordinary heart muscle fibres, or they may contain fibres from the auriculoventricular bundle. These fibres have been studied by Tawara,[2] who gives a review of the literature, and by Mönckeberg.[3] They are explained by the latter, as an irregular differentiation of the spongy musculature of the embryonic ventricle, which may or may not contain Purkinje fibres according to their distribution. Such abnormal chordæ may cause loud musical murmurs. A case in point is related by Hamilton.[4] The patient was a man of forty with symptoms of aortic insufficiency, who presented, in addition to a soft diastolic murmur with the localization characteristic of this lesion, a second murmur, also diastolic, but musical in character, which had its maximum intensity at the third left interspace, but was widely propagated over the chest, and was so loud as to be audible two feet away from the patient. The autopsy, performed by Adami, showed this musical murmur to have been produced by an anomalous cord which sprang from a small papillary muscle of its own, and crossed the auricular surface of the aortic cusp. The aortic valves were thickened and incompetent.

Anomalous chordæ passing from the aortic cusps to the base of the aorta (Rohrle), and from pulmonary cusp to base of pulmonary artery

[1] *Trans. Path Soc. Lond.*, 1880, xxxi, 63.
[2] *Ziegler's Beitr.*, 1906, xxxix, 563.
[3] *Verhand. XII Deut. Path. Gesell*, 1908, p. 160.
[4] *Montreal Med. Jour.*, 1899, xxviii, 508.

(Poscharissky) and from left auricle to left ventricle through the mitral orifice, have been recorded.

FIG. 23

Aberrant chordæ tendineæ in left ventricle producing a loud musical diastolic murmur. (From a specimen in the McGill Medical Museum, presented by W. F. Hamilton and J. G. Adami.)

DEFECTS OF THE INTERAURICULAR SEPTUM.

These may consist of a simple patency of the foramen ovale, or true defects of the interauricular septum, situated above or below the foramen, and single or multiple, may occur. In this series, the foramen ovale was patent 192 times, and there were 46 true interauricular defects, of which 15 were in its upper and 18 in its lower part, and 13 were multiple. In 14 cases the septum was rudimentary and in 5 it was absent (cor biventriloculare).

Patent Foramen Ovale.—This orifice, which in the fetus is widely open, allowing of the passage into the systemic circulation of aërated placental blood, usually closes after birth, but its persistence in adult life as a valvular slit is so common that this can scarcely be considered abnormal. Among 711 adults, Zahn found the foramen open in 139, and in Adami's records of 1374 autopsies at the Royal Victoria Hospital, Montreal, it occurred 199 times (14.5 per cent.). From the combined statistics of Bizot, Ogle, Klob, Wallman, Rostan and Hinze, we learn that among 2087 hearts examined, the foramen was patent 632 times (30 per cent.) (Herxheimer).

A widely patent foramen is, however, a true anomaly, which, by allowing free communication between the auricles, may give rise to various disturbances. Of the 191 cases in this series, 89 were of this type, and of these, 18 were instances of pure patency, unassociated with other defect, and were therefore classed as the primary lesson, as affording material for the study of special symptoms and signs. In some cases the opening is very large, the size of a "two-shilling piece" (Peacock), in others it is a "circular opening with thickened edges admitting a penhandle," and in others again, it is valvular in form but an elliptical gap remains between the concave free margins of the annulus ovalis and the valvula foraminis ovalis, which are here incomplete.

The causes of patency may lie in a rise of pressure in the right chamber after birth, preventing the firm apposition of the valvula foraminis ovalis from the side of the left auricle, and its subsequent closure; this is the case in the majority of the cases complicating other defects, such as pulmonary stenosis. Or the foramen may remain open as a result of a true arrest of growth of the primitive septa, especially of the septum secundum, an event which may be shown in the specimen by an incomplete development, absence, or fenestration of the annulus ovalis. The association of an anomalous network springing from the Thebesian or Eustachian valve, with a patent foramen or perforated valvula foraminis ovalis, and the dependence of both anomalies on the persistence of the embryonic sinus-valvular apparatus, has been mentioned. Persistence of the left superior vena cava belongs to the same complex, as is illustrated by its occurrence in the case of Berthel.

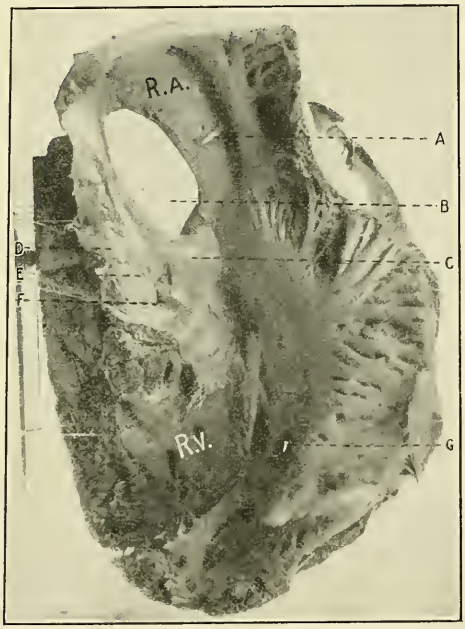
Such a combination is well illustrated in a remarkable case in the McGill Museum from the service of C. F. Martin. The patient was a woman of thirty-eight, presenting the symptoms of mitral stenosis with auricular fibrillation, and a greatly dilated heart. At the autopsy the mitral valve was markedly stenosed and the foramen was widely patent, a permanent elliptical opening 2.5 x 1.5 cm. large, with calcified lower border existing. The auricular septum behind this was greatly thinned and dilated and was bordered in the right auricle by a flattened and much fenestrated ring representing the defective annulus ovalis, and the Thebesian valve was enlarged and retiform. On the side of the left auricle at the right posterior margin of the septum, there was a curious valvular-looking pocket 2 cm. deep, the free margins of which were attached to the auricular wall by a plexus of tendinous cords. At the foot of this pocket a channel could be traced by a fine probe which communicated with the right auricle above the Eustachian valve. The coronary sinus and veins were hugely dilated.

Defects in the Upper and Posterior Part of the Interauricular Septum.—These are extremely rare. Two types may be distinguished, one in which the defect is associated with an anomalous disposition of the great veins, which is probably the primary condition, and another in which no such associated anomaly has been demonstrated, and which on closer investigation may be found to belong in the same category with the first, or which may require a different explanation. A series of cases has been recorded, in which a large defect occupies the upper margin

of the auricular septum, directly under the orifice of the superior vena cava, which is displaced somewhat to the right, so that its orifice looks into both auricles through the defect. A displacement to the right of the pulmonary veins, so that these enter either the superior vena cava just before this vessel reaches the heart, or the right auricle itself, has been noted and is to be considered the primary anomaly. Paltauf thought that the hole in the septum was not a defect at all, but represented the orifice of the right pulmonary vein, which entered here directly above the septum, with the superior cava. In Hepburn's case the wall of the auricles was directly continuous with the wall of these two veins, which here entered the auricle together. The foramen ovale was patent in some cases, and is mentioned as closed in others.

Rokitansky described 7 cases of a similar anomaly, in which the *inferior cava* looked into both auricles through the defect. In one of these the right pulmonary veins entered the right auricle.

Fig. 24



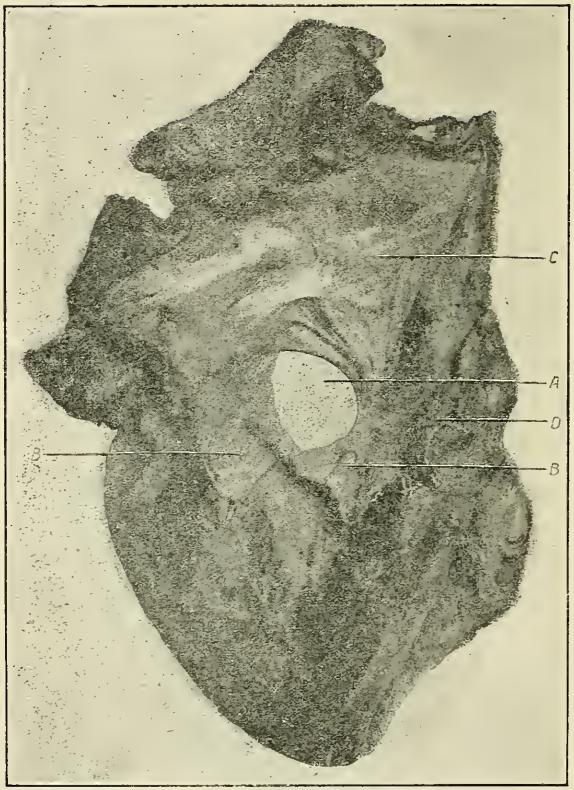
Defect in the upper part of interauricular septum (persistent ostium secundum), with pulmonary dilatation, sclerosing pulmonary endocarditis with calcification, and hypoplasia of the aorta. From a woman, aged sixty-four years. Right chambers laid open to show: *A*, hypertrophied and dilated right auricle; *B*, large defect in the upper part of interauricular septum bounded below by *C*, a stout muscular partition, the defective auricular septum; *D*, absence of annulus ovalis and of Eustachian valve; *E*, dilated coronary sinus guarded by a defective valve of Thebesius; *F*, entrance of superior vena cava; *G*, entrance of inferior vena cava. (From a specimen in the Medical Museum of McGill Univeristy, Montreal. Presented by F. W. C. Mohr. Reported by M. E. Abbott and J. Kaufmann.)

In a specimen in the McGill Museum, reported by Abbott and Kaufmann[1] (see Fig. 24), a large ovoid defect 3 x 3.5 cm. in diameter occupies

[1] *Jour. Path. and Bacteriol.*, 1910, xiv, 525.

the upper and back part of the septum, but the superior cava is not displaced, but enters the right auricle in its normal situation and is separated from the defect by a strong muscular cushion. The position of the right pulmonary veins could not be ascertained, but the annulus ovalis and Eustachian valve are absent, and it is probable that we are here dealing with an entirely different condition, namely, a huge persistent ostium secundum (patent foramen ovale) which has escaped closure

Fig. 25



Heart showing (*A*) defect of interauricular septum below (persistent ostium primum), with (*B*) cleavage of right anterior segment of mitral valve. (*C*) Interauricular septum above showing closed foramen ovale. (*D*) Left posterior mitral segment. From a woman, aged thirty-two years, without cardiac symptoms, dying of perforative appendicitis. (From a specimen in the Pathological Museum, McGill University.)

through lack of development of the secondary septum. The heart was from a woman of sixty-four in good health until the last six years of life, when cyanosis began to manifest itself. The case terminated with failing compensation and profound cyanosis, and is further remarkable in that extensive endarteritic changes with extreme calcification had taken place in the pulmonary valves, as the result of the excess of work done by the pulmonary circulation.

Defects in the Lower Part of the Interauricular Septum.—These are somewhat more frequent than are defects at the upper part of the septum, but are also rare. They are explained as a persistence of the *ostium primum*, the septum primum having failed to descend and unite with the cushion between the auriculoventricular orifice. Such a defect has a very characteristic appearance. It lies directly above the ventricles, may be of very large size, and is of a crescentic or semilunar shape, the thin border of the auricular septum, which forms its upper boundary, arching across the venous ostia to join the lower margin formed by the bases of the mitral and tricuspid valves, which are commonly deformed.

A common and interesting associated anomaly is a division of the anterior segment of the mitral valve, which is cleft from its free border up to its insertion, the two parts converging here to an acute angle, being widely separated below. In five of the seven cases of this defect reported by Rokitansky this cleavage occurred. It is well seen in Fig. 25, from a specimen in the McGill Museum. Here the foramen ovale was closed, as in the cases reported by Griffith,[1] Soldner,[2] Moore,[3] and Peacock.[4] It was patent in the cases by Reineboth,[5] Thomson,[6] Kilduffe,[7] and Sternberg.[8]

Multiple Defects.—The valvula foraminis ovalis is not infrequently perforated by numerous small openings, as in a specimen (Fig. 26) in the McGill Museum, and in several cases in this series. This recalls the fenestrated septum seen in birds, and suggests an arrest of development at this stage. In a case reported by Dublitzhaja, of combined defects of the auricular and ventricular septa, the auricular septum, defective below, "hung like a curtain over the common ventricle," there was a large patent foramen ovale, and also a large hole at the upper and posterior border of the valvula foraminis ovalis. An almost identical case is reported by Ebbinghaus. In a man of fifty-two, there were fifteen small perforations and two large holes at either border, representing the persistent ostium primum and secundum (patent foramen ovale), and the right auricle contained an anomalous network.

Aneurismal Pouching.—Aneurismal pouching of the fossa ovalis is sometimes seen (Figs. 26 and 27). In most cases the convexity of the pouch is toward the left auricle, indicating a rise of pressure in the right heart before death.

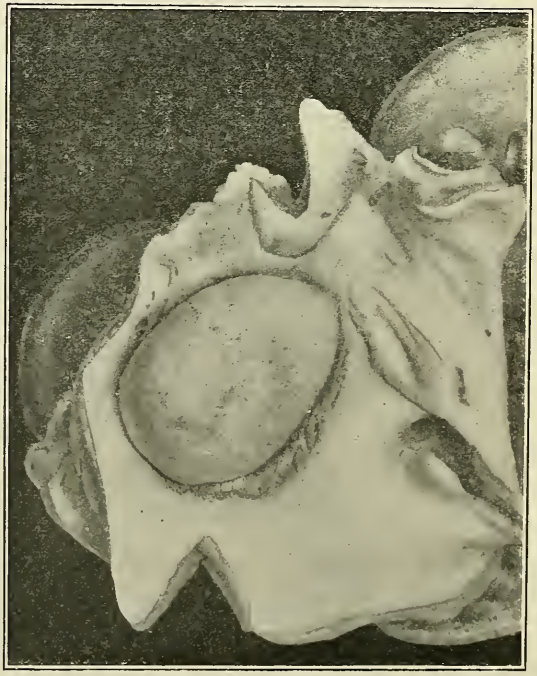
Secondary Pathological Changes.—The alterations in the circulation produced by large defects in the interauricular septum induce various secondary results. Hypoplasia of the aorta and a corresponding dilatation of the pulmonary artery are common, and the latter vessel may also be atheromatous from excessive strain. Hypertrophy and dilatation of the heart are the rule, and this may be confined to the right chambers

[1] *Manch. Med. Chron.*, 1902, iv, 383.
[2] *Munich Thesis*, 1904.
[3] *Trans. Path. Soc.*, London, 1881, xxxii, 37.
[4] *Ibid.*, 1847, i, 61.
[5] *Deut. med. Woch.*, 1895, xxi, 870.
[6] *Proc. Anat. Soc.*, 1902–3, xxxvi.
[7] *Am. Jour. Med. Sc.*, 1914, cxlvii, 880.
[8] *XVI Verh. d. Deut. Gesell.*, 1913, p. 253

FIG. 26

Fenestrated membrane bulging into fossa ovalis. (From a specimen in the Pathological Museum, McGill University.)

FIG. 27



Bulging of fossa ovalis into left auricle. Valvular patent foramen ovale. (From a specimen in the McGill Pathological Museum.)

or may be generalized, the changes in the right side almost always preponderating. In none of the cases in this series was the left ventricle hypertrophied in excess of the right. Both auricles are usually much dilated and in four of our cases this took place without any increase in size of the ventricles. Congestive changes and œdema of the lungs, enlargement of the liver, and passive congestion of all organs usually occur as late results of the overloading of the pulmonary circulation.

Symptoms and Signs.—Large defects in the interauricular septum may exist without giving any sign or symptom of their presence and without interfering with the duration of life of the individual. The characteristic feature of the majority of the cases may be summed up as an absence or but very slight manifestation of cyanosis, in the presence of distinctive physical signs of the defect. In a few rare instances, symptoms of congenital cyanosis have set in, in cases of uncomplicated foramen ovale in very early life. There are three such in our series, one by Johnson, of a man aged twenty-seven with moderate cyanosis and slight clubbing, and the others by Simmons[1] and Foster[2] in infants, showing cyanosis and dyspnœic attacks.

The above statement is especially true of defects at the *upper part* of the septum. All the patients in this series reached middle life without giving any evidence of disease, and with the exception of two cases, all died of independent conditions unassociated with the defect. In Greenfield's case, a man, aged fifty-three years, failing compensation set in eighteen months before death and cyanosis was marked at the close.

Not infrequently symptoms first develop after some event, such as an intercurrent pneumonia, has embarrassed the pulmonary circulation, and thus caused a rise of pressure in the right auricle, followed by a passage of venous blood from right to left through the defect. The picture is usually that of a relative mitral insufficiency, with marked cyanosis supervening as a terminal event. These are the cases of *la cyanosé tardive* described by Bard and Curtillet as characteristic of auricular septal defects. The hypoplasia of the aorta so often associated with patent foramen probably assists in the development of failing compensation, and therefore forms an essential part of the picture.

Auricular septal defects are not infrequently associated with mitral stenosis. Such cases, of which there are seven in our series, usually run their course under the guise of the complicating mitral condition, the defect probably adding a factor in the development of the cardiac distress. An example of the absence of characteristic symptoms in extensive communication between the auricles is seen in Dr. Martin's case of mitral stenosis with open foramen. The clinical picture here was that of the terminal stages of uncomplicated mitral stenosis, and the degree of cyanosis was not greater than might have been expected in such a condition. A presystolic thrill with maximum intensity at the left fourth interspace, and a presystolic murmur audible towards the base which disappeared as the end approached, were the only evidence of the defect.

[1] *Inter. Med. Jour. Austr.*, Feb. 20, 1906.
[2] *Dublin Quarterly Jour. Med.*, 1863, xxxvi, 112.

Pallor of the surface is a common characteristic (Mouls[1]) as is also a certain delicacy of build, the result evidently of the diminished amount of blood in the systemic circulation. Dyspnœa and tachycardia, bronchitis and signs of congestive changes in the lungs and of passive congestion in the viscera and enlargement of the liver are also common, from excess of blood entering the right heart. When, in adults with these symptoms, and with cyanosis slight, absent, or of extremely late appearance, we find distinctive physical signs of a defect localized over the upper and middle thirds of the heart, we may feel fairly sure that we are dealing with an auricular septal defect. A correct diagnosis was made on this basis in a patient at the Royal Victoria Hospital whose heart is in the McGill Museum. In a woman of twenty-eight years, of somewhat infantile appearance, in whom cyanosis was entirely absent, a loud harsh systolic murmur with maximum intensity at the third left interspace, 4.5 cm. from the midsternum, was heard loudly all over the front of the chest and over the left back, the cardiac dulness was greatly increased in all directions, and there was a marked systolic thrill at the base to the left of the midsternum, extending downward to the top of the fourth rib. The neck veins were much distended, but no positive venous pulse was detected. Death occurred from chronic interstitial nephritis. The autopsy showed a large patent foramen ovale admitting the thumb, with cribriform perforation of the valvula foraminis ovalis, hypoplasia and slight coarctation of the aorta, and infantile genitalia.

The slight degree of cyanosis that characterizes these cases and the effect of the lesion upon the duration of life are well shown by the analysis of the 43 cases of auricular septal defects classified as the primary lesion in this series. Cyanosis was *entirely absent* in 21 cases. In 2 of these death apparently due to the defect occurred in 4, in 2 cases from failing compensation, in 1 from sudden collapse, and in 1 (Popper[2]) by sudden development of œdema and dyspnœa. *Terminal cyanosis* occurred in 13 cases of the series. The ages of the patients ranged from ten to sixty-four years, and death ocurred from pneumonia in 2, from failing compensation in 6, and from cerebral hemorrhage in 1 (Ebbinghaus). In 4 other cases of the 43, cyanosis was described as *slight* and in 3 only as *moderate* (Johnson, Foster, Simmons).

Physical signs are sometimes absent, but, in widely patent foramen ovale, and in defects at the lower part of the septum, a sufficiently characteristic murmur is usually present, and sometimes a corresponding precordial thrill. In defects at the lower part of the septum in which extensive deformities of the auriculoventricular cusps are usually associated, the murmur produced is often heard best at the apex, and is "confused," or "roaring" in character. It was associated in 4 out of 10 cases analyzed with a thrill continuous or systolic or "presystolic" in rhythm. In widely *patent foramen*, the murmur is usually systolic or presystolic and is sometimes soft, but often harsh and rasping, or of a peculiar blowing, or even musical character, and may be localized in the second,

[1] *Rev. Mens. des Mal. des Enfant*, 1888, vi, p. 151.
[2] *Wien. klin. Woch.*, 1909, No. 16, p. 562.

third or fourth interspace near the left sternal border, or over the mid-sternum in this situation, or may be diffusely heard over the precordium. It is *frequently audible in the left back*, and may be transmitted to the apex and axilla, or (occasionally) to the left subclavicular region (Markham's[1] case), or may be heard loudly over the whole chest. Among the 18 cases of patent foramen analyzed, a murmur of the above character was noted in 14. In 9 it was systolic, in 3 presystolic, in 2 it varied from presystolic to systolic, and in 1 only (Bard and Curtillet) it was diastolic in rhythm. In 3 of these cases the murmur was associated with a thrill of corresponding localization and rhythm.

Both murmur and thrill may vary in intensity and in rhythm with the position of the patient being noted as presystolic or systolic on different examinations. This inconstancy may be a useful diagnostic point (Ohm).

When an organic mitral insufficiency is combined with a patent foramen, the regurgitation of blood through the defect into the right auricle during systole of the ventricles may give rise to a *positive venous pulse* in the neck, without the presence of tricuspid insufficiency. Cases are reported, confirmed by autopsy, in which the tricuspid was healthy, and in which no signs of tricuspid regurgitation existed during life. When mitral stenosis is present this sign is of no value, as it is likely to be due to the auricular fibrillation so frequent in this condition.

Paradoxical Embolism.—A serious clinical significance is given to patent foramen ovale by the fact that particles may be carried through the defect from the venous circulation to the arteries of the brain, or from the systemic arteries to the lung, leading to instant death. This possibility was first pointed out by Cohnheim in an observation of a woman dying of embolism of the middle cerebral artery. The foramen admitted three fingers, the arterial system was clear, while the primary thrombi lay in the veins of the lower extremities. Ohm[2] collected 11 such cases from the literature in which an embolus from a thrombosed vessel or a metastasis from a new growth undoubtedly passed through the open foramen and added an original case. Ballet[3] collected 6 cases of death from cerebral abscess from infected emboli in which both cardiac and cerebral symptoms were present during life. In 3 of these there was a patent foramen, in 2 a defect of the interventricular septum. Verse[4] described 2 typical cases.

DEFECTS OF THE INTERVENTRICULAR SEPTUM.

The interventricular septum may be completely absent (cor biatriatrum triloculare), or it may be rudimentary, represented by a falciform process growing up from the lower and anterior wall of the ventricle, or localized defects may occur. These usually lie at its base, and are relatively common in association with other anomalies, but are not frequent alone. Defects elsewhere than at the base, whether alone or in combination, are among the rarest of cardiac anomalies.

[1] *Trans. Path. Soc.*, London, 1881, viii, 142.
[2] *Zeit. f. klin. Med.*, 1907, lxii, 374.
[3] *Archiv. gén. de. méd.*, 1880.
[4] *XIII Verh. Deut. Path. Gesell*, 1909, p. 215.

Defects at the Base.—The cases of congenital cardiac disease here studied have been drawn only from reliable sources, and all have post-mortem reports attached, which should make them a fair index of relative frequency. It is therefore of interest to note that among them, while defects elsewhere in the septum are exceedingly rare, "pure" defects at the base are commoner than is usually supposed, and, in combination with other defects they rank as the most frequent cardiac anomaly.

Among the 631 cases, a defect at the base occurred 177 times, elsewhere than at the base, 12 times, making 189 cases, or 30 per cent. Of the 177 defects at the base, 34 were classed as the primary defect and 143 complicated other conditions. Of the 34 "primary" defects at the base, 8 were combined with *rechtslage* of the aorta, and in 1 of these there was also pulmonary hypoplasia; in another there was pulmonary hypoplasia without *rechtslage;* in 3 there was a patent ductus arteriosus, leaving 22 "pure" defects at the base unassociated with *rechtslage* or other anomaly except (in 5 cases) bicuspid or defective aortic or pulmonary valves.

Of the 143 defects at the base complicating other anomalies, 75 were in cases of pulmonary stenosis or atresia, in 53 of which there was also *rechtslage* of the aorta. Of the remainder, 26 were in transposition of the great trunks, 3 in other defects complicated by *rechtslage,* and 13 in persistent truncus arteriosus. That is to say, in 42 other cases the defect was associated with an irregularity of development of the great trunks. In the remaining 26 of these 143 cases, the septal defect was associated with tricuspid atresia in 9 cases, with mitral atresia in 1, with aortic stenosis or dextrocardia in 2, and with partial defect of the aortic septum in two.

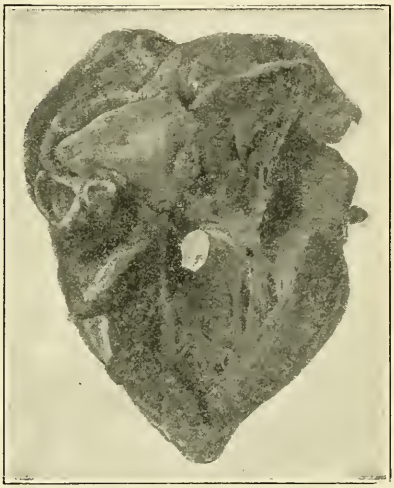
Pathogenesis.—The combination of a defect of the interventricular septum with pulmonary stenosis and *rechtslage* of the aorta constitutes one of the commonest forms of congenital cardiac disease. So frequent is the combination that a causal connection between the three conditions has been sought, and rival theories as to which is the primary lesion have been suggested.

Much light was thrown upon this subject by Rokitansky, who concluded that non-inflammatory pulmonary stenosis, displacement to the right of the aorta, transposition of the great arterial trunks, and defects at the base of the interventricular septum were alike dependent upon a common cause, a deviation of the aortic, so that it failed to unite with the interventricular septum. He divided the latter into a part anterior, and one posterior to the undefended space, and classified defects at the base according as they lay in the anterior part of the anterior septum, in the posterior part of the anterior septum, or in the posterior septum. He pointed out that their usual situation was in the "posterior part of the anterior septum," that is, just anterior to the pars membranacea, in which case he believed they were practically invariably associated with a malposition of the arterial trunks. Keith has suggested that in the large number of cases in which a septal defect is associated with stenosis of the conus of the right ventricle the defect is a direct

result of the inadequate expansion of the bulbus cordis to form the infundibulum of the right ventricle.

Later advances in embryological knowledge show that the aortic septum is prolonged downward to assist in closing the interventricular septum at the undefended space, instead of the interventricular septum growing upward to form part of the aortic wall, as Rokitansky supposed. Moreover, independent defects of the interventricular septum in this situation, unassociated with any alterations in the relations of the great arterial trunks, and evidently not of inflammatory origin, may and do occur. This is so in the specimen seen in Fig. 28, and in cases reported by Orth,[1] Arnold, Preisz,[2] and Hart.[3] Such conditions cannot be explained on Rokitansky's theory as due to deviation of the septum, or, a deficient expansion of the infundibulum, but are due, as Keith himself points out, to a primary arrest of growth of unknown origin. In Hart's case an interesting associated anomaly, which may have had some bearing on the defect, was an anomalous cord which extended from the lower border of the conus of the right ventricle through the septal opening, to the anterior segment of the mitral valve.

FIG. 28



Defect of the interventricular septum at undefended space. Heart of infant. No other anomaly. (From a specimen in the McGill Pathological Museum.)

Pathology.—The commonest situation for the defect is directly beneath the aortic cusps and just anterior to the undefended space (Rokitansky's posterior part of the anterior septum) (Fig. 28). Here it lies with the fleshy muscular septum before it and the thin pars membranacea behind, and opens in the right heart beneath the septal cusp of the tricuspid, sometimes perforating this or bulging the (adherent) tricuspid leaflet before it, or opening into the right auricle directly above the base of the tricuspid, thus establishing a communication between this cavity and the two ventricles. More rarely the defect is placed farther forward in the septum in its anterior fleshy part, just behind the front wall of the heart, and is separated behind from the undefended space by a muscular column, opening into the conus of the right ventricle below the pulmonary valves. (Rokitansky's anterior part of the anterior septum). Examples are the cases by Coupland[4] and Rolleston.[5] Keith points out that in these cases, the defect is evidently in the musculature of the interbulbar septum, *i. e.*, it is in that part of the interventricular septum

[1] *Virchows Archiv*, 1880, Bd. 82, 529.
[2] *Ziegler's Beiträge*, 1890, Bd. 7, 245.
[3] *Virchows Archiv*, 1905, Bd. 181, p. 73.
[4] *Trans. Path. Soc. London*, 1879, xxx, 226.
[5] *Ibid.*, 1891, xlii, 65.

which in the embryo formed the proximal part of the bulbus cordis before its division into the conus of the pulmonary artery and the vestibule of the aorta.

The defect varies in form and size from a pinhead perforation with tendinous edges, a round or oval hole admitting a goose-quill, knitting needle, index finger, etc., to a large triangular, semilunar, or crescentic space with thick-walled lower muscular border. Aneurismal pouching of the pars membranacea into the right ventricle may occur, with multiple sacculations perforated at their apices at one or more points (*vide infra*).

Quite frequently the margins of the defect with the adjacent valves are the seat of an acute inflammatory process which apparently originates at this point, because, as the seat of greatest strain, it affords a site of lowered resistance. Such a case is reported by Gordon.[1] In a boy aged five years who died of malignant endocarditis, a marked precordial thrill, and loud, harsh systolic murmur over the whole chest, with maximum intensity at the third and fourth left cartilages, indicated the septal defect. The autopsy showed a congenital opening, admitting a lead pencil, between the ventricles. The pulmonary valves and adjacent wall of the right ventricle were the seat of a number of large grayish-green vegetations which extended below the level of the interventricular opening.

Moschcowitz[2] related a very similar finding in a woman of twenty-nine years, who had had cardiac symptoms, palpitation, dyspnœa and occasional œdema of the legs since her fifteenth year, with exacerbation during the last four months, and symptoms of acute infection with chills and septic fever for one week. The blood cultures on one occasion showed *Streptococcus viridans*. At the autopsy both ventricles were hypertrophied, and the right also dilated, and there was a defect in the membranous septum admitting a lead-pencil. The pulmonary valves were replaced by large gray pedunculated vegetations, which extended up the wall of the pulmonary artery to its bifurcation, and had led to multiple emboli in either lung. The prolonged history of cardiac symptoms without adequate cause suggested a congenital lesion upon which the malignant endocarditis had been engrafted.

Dr. W. Thalhimer has sent me photographs of a heart from a cyanotic boy of nine years, with a huge septal defect and pulmonary stenosis in which a vegetative process had developed along the line of closure of the mitral and tricuspid valves. As there was no clinical history of an infective process, no Aschoff bodies in the myocardium, and no evidences of bacteria in the vegetations on microscopic examination, he is inclined to explain the vegetations on the ground of mechanical strain by the unnatural whirls in the blood stream, which have caused microscopic injuries of the valves and have thus given rise to an aseptic thrombosis. From a statistical study of the literature one is led to conclude that, at least in a large proportion of cases, the infective nature of the inflammatory process, so common in the neighborhood of cardiac defects, has been demonstrated.

[1] *Brit. Med. Journ.*, 1897, ii, 1174. [2] *Proc. New York Path. Soc.*, 1914, xiv, 18.

In a case reported by Hebb[1] of a girl, aged eighteen years, whose heart showed a funnel-shaped defect at the base of the septum admitting a goose-quill, there were large vegetations on the aortic, mitral, and pulmonary valves, and a *patch of vegetations was also situated on the wall of the right ventricle opposite the defect.* This observation, which is repeated in several other cases, as well as the frequent localization of the vegetations in the right ventricle affords an interesting proof of the fact that under normal conditions the current of blood flows from the left ventricle to the right through the defect. It is natural to suppose that this would be so, for the pressure in the systemic circulation is normally higher than it is in the pulmonary. Further anatomical confirmation of this direction of the stream is afforded by the oblique direction and funnel-shape, with its larger end toward the left ventricle which the opening often assumes, and also by the not infrequent occurrence of patches of fibrosis on the opposite wall of the right ventricle.

Septal defects may exist without producing any change in the heart chambers, but they lead, still more frequently than do defects of the interauricular septum, to hypertrophy and dilatation of both ventricles. Where the defect is combined with *rechtslage* of the aorta, marked hypertrophy of the right ventricle is a constant feature. The pulmonary artery may be markedly dilated, as in 9 cases of the 34 "primary" defects at the base.

The distribution of the auriculoventricular junctional bundle in septal defects is of much interest, and has been investigated by Keith, Mönckeberg, Morison,[2] and others. As is well known this bundle emerges from the auriculoventricular node close to the interauricular septum behind the medial cusp of the tricuspid valve, and divides into two branches, the left of which pierces the interventricular septum just in front of the pars membranacea, and passes downward superficially beneath the endocardium of the septum to be distributed to the papillary muscles and columnæ carneæ of this chamber, while the right branch runs, more deeply imbedded in the musculature of the right side of the septum, to the apex of the right ventricle. In most of the cases of septal defect examined there was surprisingly little change in this normal arrangement, the fibres streaming over the free border of the septum that formed the base of the defect toward the apices of their respective ventricles. In Morison's case the left branch was abortive. Keith described an abnormal band of "subaortic musculature," which may develop in the pars membranacea and overlie the bundle as it courses down the surface of the septum in the left ventricle, and in one of Mönckeberg's cases of septal defect the bundle lay deeply in the musculature of the left septum instead of sub-endocardially as normally occurs. Recent investigations by Flack and Mall have shown that the interventricular septum is formed, not by a process growing upward from below, as Rokitansky supposed, but by a hollowing out of the spongy musculature of the embryonic ventricle to form the right and left chambers; the tip of the inferior septum, therefore, represents the wall

[1] *Trans. Path. Soc. London*, 1897, xlviii, 41.
[2] *Jour. Anat. and Physiol.*, 1913, xlvii, 459.

of the lumen of the original cardiac tube, and this may account for the persistence of the bundle at this point in septal defects.

Symptoms and Physical Signs of Septal Defects.—These may be absent and the defect discovered at autopsy. When cyanosis is present it may be slight or transient, appearing only on exertion, or terminal at the end of a long life, or, more rarely, and usually in those cases associated with *rechtslage* of the aorta, it may be well marked. Among the 34 "primary" defects at the base there was an entire absence of cyanosis in 17; it was slight in 5, moderate in 2, marked in 3, and terminal in 4 cases.

Physical signs may also be absent, as in two otherwise normal hearts with defects admitting a goose-quill, in the McGill Museum. On the other hand, physical signs atypical of acquired valvular disease are often present, even in the absence of symptoms, and are frequently sufficiently characteristic to permit of a diagnosis being made. In pronounced cases there may be visible pulsation and precordial bulging, and a thrill, usually systolic in time and diffuse over the precordium, or most marked over the middle of the cardia, is common and is more frequent than in auricular septal defects. A thrill was present in no less than 11 of the 34 cases of primary defects at the base; in 10 being systolic and in 1 a "continuous vibration." In 7 it was diffused over the whole cardia; in 3 it was most marked over its upper half; in 2 others it was localized at the apex.

A harsh, systolic murmur localized in the third or fourth left space is the most frequent evidence of the defect. Sometimes a very small hole may be accompanied by a very loud murmur. Roger described as characteristic a "single long, constant murmur beginning with systole and continuing through both heart sounds, localized in the upper third of the precordial region." Reiss mentions as typical a loud systolic murmur in the middle of the precordium, localized over the inner part of the third left space and the fourth rib.

A murmur apparently due to the defect was present in 26 of the 34 cases. In those in which its character was specified it was loud in 18, rough in 3, whistling, grating, harsh, sawing, each in 1, rasping in 3; in 3 instances it was blowing. It was systolic in rhythm in all 26 cases, and in 3 of these a diastolic murmur was present as well. The point of maximum intensity was 12 times in the upper third of the precordium near the left sternal border; of these, in 4 it was stated to be at the third left space, in 2 others also at the fourth left space, in 2 at the third costal cartilage (in 1 of which it was heard with equal intensity at the apex), in 2 at the pulmonary cartilage and second left space, and in 1 "over the middle of the sternum opposite the third left interspace." Besides these, in 2 other cases it was "along the left sternal border," "just to the left of the xiphoid cartilage," and "at the aortic cartilage;" in 2 (in 1 of which it was associated with *rechtslage*) it was "loudest at the apex," and in 4 it was diffuse over the precordium.

The murmur is usually transmitted downward along the left sternal border, and is frequently heard behind in the left infrascapular region. It may be diffused over the whole precordium, but is usually not heard in the axilla nor below the clavicle. In 6 cases in this series it was so

loud as to be heard over the whole chest, and in 2 cases it could be traced into the vessels of the neck.

Eisenmenger[1] claimed that a systolic murmur produced by the defect may be transmitted along the aorta, and thus be heard in the vessels of the neck, when pulmonary hypoplasia is also present, in which case the blood is diverted by the obstruction from its usual course into this vessel, and so passes from right to left into the aorta. In his own case, diagnosed by Schrötter before death, there was a defect admitting the thumb in the posterior part of the anterior septum, with *rechtslage* of the aorta and a dilated pulmonary artery. The patient, a man aged thirty-two years, had had cyanosis and dyspnœa from birth. There was visible precordial pulsation and bulging, and a systolic murmur over the middle of the heart transmitted everywhere over its surface, but chiefly to the right and inferiorly, not heard above its base, along the course of the aorta nor in the pulmonary artery, the latter vessel being too far below the surface to transmit the sound.

Aneurisms of the Undefended Space.—Cases have been recorded by Rokitansky, Zahn,[2] Hart,[3] MacCallum,[4] and others, in which, in the absence of any evidence of endocarditis, sacculations, single or multilocular, of the membranous portion of the septum project into the right auricle above the medial cusp of the tricuspid, and in some cases extend also into the musculature of the interventricular septum. Malignant endocarditis of the bulging area is not infrequent and rupture into the right auricle may occur. On this ground it has been argued[5] that these aneurisms are not of congenital origin, but are due to the action of the inflammatory process upon this delicate part of the septum. As was pointed out by Rokitansky, however, the reverse is probably true, the aneurism supplying a nidus of lowered resistance upon which an infective process has been secondarily engrafted. This point has been made the subject of an interesting communication by Mall,[6] who pronounces definitely upon the congenital and non-inflammatory origin of these aneurisms, and shows the cause to be a malposition of the inferior septum (inferior septum proper) so that "the membranous septum develops improperly and becomes placed in a horizontal position, and is thus weakened in every way, and predisposed to the formation of aneurisms." In his own case the membranous septum was cribriform, and the hole communicated with numerous sacs in the medial segment of the tricuspid, and also bulged into the right atrium.

Such aneurisms may give rise to marked and characteristic physical signs. This was true of two remarkable cases, one a heart which is in the McGill Museum, the other reported by Tate,[7] in which a trumpet-shaped tube, which formed the apex of a saccular pouching of the pars membranacea, projected behind and perforated the medial cusp of the tricuspid valve; in the McGill specimen there was malignant endocarditis of the immediately adjacent tricuspid segment.

[1] *Zeitschr. f. klin. Med.*, 1897, xxxii, Supp. Heft, 1.
[2] *Virchows Arch.*, 1878, lxxii, 206.
[3] *Ibid.*, 1905, clxxxi, 51.
[4] *Johns Hopkins Hosp. Bull.*, 1900, xi, 69.
[5] Buhl, *Zeits. f. Biol.*, 1880, xvi.
[6] *Anat. Record*, June, 1912, p. 2921.
[7] *Trans. Path. Soc. London*, 1892, xliii, 36.

The relative frequency of *aneurisms of the right aortic sinus of Valsalva* and the probable dependence of these upon the juxtaposition of the pars membranacea of the right aortic cusp, has been discussed by Hart.[1] The insertion of the medial cusp of the tricuspid just behind this point may further weaken this region by making it a seat of traction. It is not necessary to presuppose a congenital defect, although this may occur. In a case reported by Hale White[2] an oval defect admitting a No. 10 catheter lay just below the right half of the anterior aortic cusp: its edges were thickened, but the septum around it for three-quarters of an inch was thin and translucent, and the sinus of Valsalva above it was expanded into an aneurismal pouch, which protruded and burst into the right ventricle. The author thought that the whole septum between the lower part of the aorta and the base of the ventricles was abnormally thin.

Defects in the Septum Elsewhere than at the Base.—These are usually multiple, and irregular or slit-like in form. They are of the greatest rarity. This is especially true of those low down in the septum.

COMPLETE ABSENCE OR RUDIMENTARY DEVELOPMENT OF THE CARDIAC SEPTA.

A rudimentary development of the cardiac septa, leading to a diminution in the number of the heart's cavities, should not be treated entirely apart from localized septal defects, being simply a more extreme degree of the same lesion. Yet the cases may be conveniently grouped together as indicating arrest at a very early stage of embryonic life (fourth week), frequently associated with anomalies elsewhere, and as forming an altogether different and more serious picture.

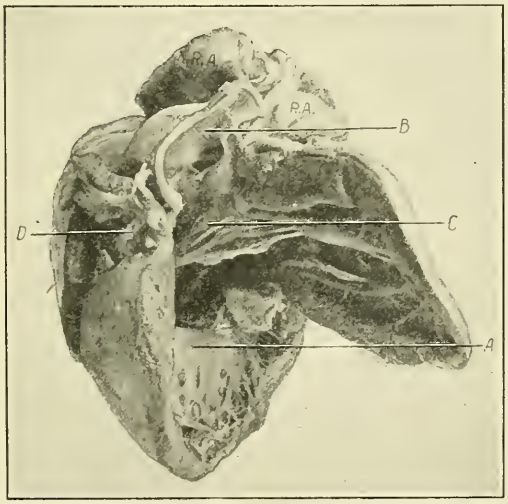
Cor Biloculare.—Early cases were recorded by Wilson in 1798, Farre in 1814, Ramsbotham in 1846, and Forster in 1847, and there are six in the recent literature by Rudolf,[3] Konstantinowitsch,[4] Gierke,[5] Schroeder,[6] Jensen,[7] and Rivet and Girard.[8] We have had an opportunity of examining the specimen recorded by Rudolf, which is in the Museum of the Toronto University. The patient was a girl of sixteen years, undeveloped and cyanotic, who suffered from marked dyspnœa and died of pulmonary tuberculosis. The auricular septum was absent and a large right was divided from a smaller left auricular portion, with corresponding auricular appendages, by a slight ridge on the posterior wall. A single large bicuspid auriculoventricular orifice opened into the left side of a single ventricle which gave off a large aorta and a smaller artery from its right side, in transposed relations, and separated from the left part of the cavity by a shallow muscular ridge, which lay in the posterior wall and marked the site of the absent interauricular septum. The pulmonary orifice was stenosed. The cases by Gierke and Konstantinowitsch were

[1] *Virchows Arch.*, 1905, clxxxii, 168.
[2] *Trans. Path. Soc. London*, 1892, xliii, 34.
[3] *Anat. Soc. of Gt. Brit. and Ire.*, Nov., 1899.
[4] *Prag. Med. Woch.*, 1906, p. 657.
[5] *Charité-Annalen*, 1908, xxxii, 229.
[6] *Deut. Arch. f. klin. Med.*, 1911, ccv, 122
[7] *Giessen Thesis*, 1912.
[8] *Arch. des Mal. du Cœur.*, November 11, 1913.

identical with this, except that the great vessels were not transposed and in the former the pulmonary artery was atresic, in the latter the aorta. In other cases the development of the aortic septum was completely arrested and a common arterial trunk replaced the two great vessels.

An anomalous entrance of the pulmonary veins into the superior cava, innominate, hepatic, or other veins, instead of into the left auricle, was noted in Wilson's case, and in most of those recently reported. In that by Rivet and Girard, of a cyanotic infant aged twenty-five days with polycythemia, these veins formed a common trunk which ended in the lobus spigelii of the liver, and anastomosed here with the venæ cavæ and portæ. It seems possible that this anomaly may be the primary one, at least as regards the non-development of the auricular septum, for comparative anatomy shows that differentiation of the auricles is evolved during the formation of a pulmonary circulation.

FIG. 29



"Incomplete double heart," showing (*A*) the interventricular septum, defective in its upper half; *B*, a large, thick-walled aorta, arising from both ventricles above the defect; *C*, a single auriculoventricular cusp arising from both ventricles; *D*, stenosis of the conus of the pulmonary artery; *R.A.*, the enlarged right auricle. The right auricle and left ventricle are much hypertrophied and dilated; the left auricle and sinus of the right ventricle rudimentary. The interauricular septum is defective in its lower half. (From a specimen in the McGill Pathological Museum, presented by Dr. Andrewes.)

Such cases of pure biloculate heart are extremely rare. A more common form is that in which the septa are partly developed, and an incomplete division has occurred into four cavities, the organ still remaining two-chambered in the exercise of its function (incomplete double heart). A good example is shown in a specimen in the McGill Museum, presented by Dr. F. W. Andrewes (Fig. 29). Here the auricles are incompletely divided into a large right and a small left chamber, by a narrow septum having a large defect above, multiple fenestrations, and a deeply concave lower free border (persistent ostium primum). A thick muscular

septum, one inch high, with rounded free border, projects upward from the lower wall of the ventricle, partly dividing it into a small, thick-walled right, and a capacious left ventricle. A dilated aorta rides above this rudimentary septum and a narrow thin-walled bicuspid pulmonary arises from a rudimentary conus. There is a common auriculoventricular orifice with five cusps, one of which is very strong and large and arises from the opposing wall of either ventricle, stretching across above the rudimentary septum and shielding the auriculoventricular orifice from the two arterial ostia.

A third variation of biloculate or triloculate heart is presented by cases of mitral or tricuspid atresia with absent or defective auricular septum. In tricuspid atresia the ventricular septum has been developed, but a defect remains at the base through which the blood passes from the large left ventricle into the pulmonary artery through the persistent bulbus, the sinus of the right ventricle having become obliterated. An excellent example of the former condition (tricuspid atresia) is published by Robertson[1] under the title, cor biatriatrum triloculare. The auricular septum was defective below (persistent ostium primum) and an anomalous septum, evidently the persistent right valvula venosa, crossed the right auricle from the Eustachian valve, and was inserted into the base of the interauricular septum at the site of the tricuspid orifice, which was here obliterated, *possibly as a result of the insertion of the anomalous septum at this point.* The great arterial trunks were transposed, the aorta arising from the persistent bulbus arteriosus of the obliterated right ventricle, which communicated with the cavity of the left ventricle by a defect at the base of the otherwise fully developed interventricular septum. Aplasia of the left chambers in mitral atresia is described by Bernstein[2] and by Girauld and Tissier.[3] In the latter's case the left auricle was tiny, and was separated from the left ventricle by a rudimentary bicuspid valve, and a large orifice united it with the greatly dilated right auricle. The right ventricle was also enormous and gave off both the aorta and the pulmonary artery in normal relations but separated from each other by a thick muscular cushion (apparently marking the conus of the pulmonary artery).

Biloculate heart is frequently displaced to the right side of the body, in that type of dextrocardia that is apparently due to arrest of development. It is often associated with transposition of one or more viscera or other serious defects. The spleen was absent in three of the cases.

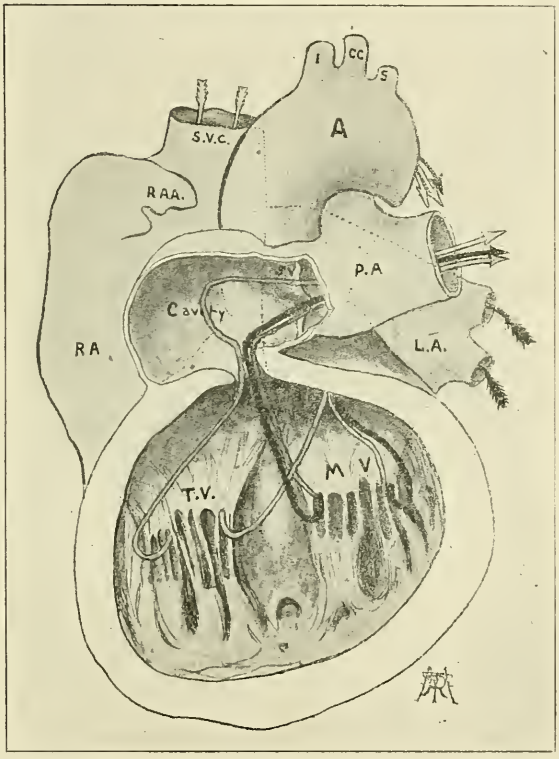
Cor Biatriatrum Triloculare.—Absence of the ventricular with presence of the auricular septum constitutes a three-chambered heart with two auricles and the tricuspid and mitral orifices opening into a common ventricle, from which (if the aortic septum develops), two arterial trunks arise. Arnold[4] reports a case of complete absence of the ventricular septum, with auricular septum defective below (persistent ostium primum), pulmonary atresia, dextrocardia, and absence of the spleen, and adds a study of 30 cases of cor biatriatrum triloculare. As in cor

[1] *Lancet*, 1911, 180, p. 872.
[2] *Proc. New York Path. Soc.*, 1906, N. S., vi, p. 29.
[3] *Bull. Soc. d'Obstet. de Paris*, 1910, xiii, 420.
[4] *Virchows Arch.*, xlii.

biloculare, obliteration of the right ventricle in tricuspid atresia (with auricular septum present) is frequently reported as triloculate heart.

A special type of anomaly has been established, of what is functionally a cor biatriatrum triloculare, although four chambers exist, by a series of cases recorded in which an anomalous septum cuts off from a common ventricle a small chamber which lies at the base of the heart and gives off one or the other of the great arterial trunks. Such a case, reported and figured by Holmes,[1] in 1824, the specimen from which is in the McGill

FIG. 30



Cor biatriatrum triloculare with malposed interventricular septum. Diagrammatic sketch by Prof. R. Tait Mackenzie, showing course of blood and relation of cavities in Dr. Andrew Holmes' case of displaced interventricular septum cutting off a small cavity which gives off the pulmonary artery. The pale line shows venous, the dark line arterial blood. (From the Medical Museum of McGill University.)

Museum, is represented diagrammatically in Fig. 30. The auricles, which were enormously dilated, especially the right, emptied their contents through their respective ostia into a common ventricle, which gave off the aorta behind and somewhat to the left and communicated through a diamond shaped opening in an anomalous septum with a small cavity at its right upper angle of the common ventricle which gave off the dilated pulmonary artery in its normal relation to the aorta. In eight

[1] *Edin. Med. Chir. Soc.*, 1824, republished by M. E. Abbott, *Montreal Med. Jour.*, 1901.

other similar cases reported by Young,[1] Peacock,[2] Rokitansky (2 cases), Chiari, Thérémin (Obs. 43), and Marchand,[3] and in a specimen which the writer has had the privilege of studying in the Museum of the Harvard Medical School, the aorta arose from the small chamber in front and to the right, and the pulmonary artery from the common ventricle behind it, the two vessels being in transposed relations. It has been suggested by Keith that in these cases the anomalous septum is the persistent lower orifice of the embryonic bulbus cordis, but study of both the McGill and Harvard specimens lead us to the conclusion, that in these specimens, at least, the strong muscular wall with a large defect at its upper border through which the small cavity communicates with the large common ventricle, is simply the malposed interventricular septum itself, which has failed to unite with the aortic septum, and has been carried around to the right in the further development of the heart.

Cor Biventriculare Triloculare.—When the auricular septum is absent and the ventricular septum present, a heart with two ventricles and a single auricle results. Such a case is reported by Williams.[4] All the blood entered the common auricle through the superior vena cava (the pulmonary veins having again an anomalous entrance).

Symptoms and Physical Signs.—In biloculate heart cyanosis is usually present from birth, and becomes very marked. The cases of Forster,[5] Ramsbotham,[6] and Crisp[7] were all typical morbus cæruleus, dying, respectively, at seventy-eight hours, ten days and ten weeks. On the other hand symptoms may be moderate, as in Turner's case, in which there was no cyanosis until just before death at the age of fifteen months. Cases of cor biatriatrum triloculare present perhaps the best illustrations we have that the admixture of venous and arterial blood is compatible with long life and with only slight disturbances of the circulation. Young's patient, who died at thirty-nine years, cyanosis having developed only within the last three weeks of life, and Peacock's almost identical case, already noted, and that by Mann,[8] dying at twenty-one years, are illustrations. Holmes' specimen (Fig. 30) was from a young man, aged twenty-four years, in whom there was only moderate cyanosis and a tendency to suffocative attacks. Physical signs may be prominent, but cannot be said to be characteristic.

DEFECTS OF THE AORTIC SEPTUM.

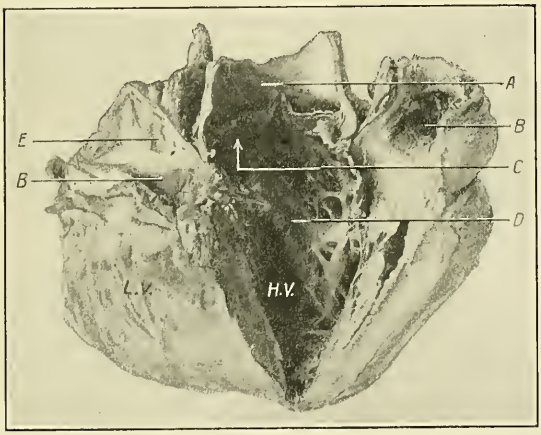
When the aortic septum fails to develop, a single large thick-walled trunk (*persistent truncus arteriosus*) results, which arches upward in the course and gives off the branches of the normal aorta, the pulmonary artery arising therefrom. This abnormality is very uncommon. Partial defect of the aortic septum is even less frequent than is its complete absence. It may result in a common trunk with early division into aorta

[1] *Jour. Anat. and Physiol.*, 1907, xli, 190.
[2] *Trans. Path. Soc.*, London, 1854, vi, 177.
[3] *Verh. d. XII Deut. path. Gesell*, 1908, p. 174.
[4] *Jour. Anat. and Physiol.*, 1894, xxviii, 305.
[5] *Trans. Path. Soc.*, 1846, i, 21.
[6] *Ibid.*, p. 21.
[7] *Trans. Path. Soc.*, London, 1859, x, 49.
[8] *Ziegler's Beitr.*, 1889, vi, 485.

and pulmonary artery and rudimentary septum within it, or, when the defect is still smaller, in an abnormal communication between the aorta and the pulmonary artery or the conus of the right ventricle.

Persistent Truncus Arteriosus (Common Arterial Trunk, Complete Defect of the Aortic Septum).—This abnormality is very uncommon, only 22 cases are available in the literature and from other sources of study. The cardiac septa are frequently rudimentary or absent, a biloculate or triloculate heart existing. When, however, these are well developed and the heart is four-chambered and otherwise normal, a localized defect at the base of the interventricular septum always remains. The common trunk either rides above it, receiving the blood equally from both ventricles, or arises more or less entirely from the right ventricle, the blood entering it from the left through the defect.

Fig. 31



Persistent truncus arteriosus. Heart of a child, aged five years, in whom cyanosis developed at one and one-half years. *A*, common arterial trunk arising entirely from right ventricle, and communicating with the left ventricle through the right auricle; *B*, right auricle laid open; *C*, defect at base of interventricular septum; *D*, heavy muscular column from wall of right ventricle to base of defect; *E*, interauricular septum seen from right auricle showing multiple defects. Heart is wider than high. (From a specimen in the McGill Pathological Museum presented by Dr. Mackenzie Forbes.)

This recalls the early stage at which the arrest of growth has occurred, when the primitive aorta is given off entirely from the right side of the common ventricle (Fig. 16). A typical specimen of this kind is shown in Fig. 31 from a specimen in the McGill Museum. The large common arterial trunk springs entirely from the right ventricle, and has three strong semilunar cusps, behind two of which the coronaries arise. Below the anterior and right posterior cusps there lies a circular defect in the septum, admitting the little finger, with rounded edges, by which the left ventricle communicated with the aorta and with the right ventricle, which is much hypertrophied; a heavy muscular column runs from the anterior wall of this ventricle to the lower border of the defect. The left auricle and ventricle are perfectly formed, but are much smaller than the right chambers. There are multiple defects in the interauricular septum. The blood supply to the lungs is unknown.

The pulmonary circulation in these cases is of the greatest interest. Two large branches, one to either lung, may arise from the wall of the common trunk some distance above its origin, as in the cases of Heath[1] and Ramsbotham. Quite commonly one pulmonary branch arises from the aorta soon after its origin, and supplies either the right or the left lung, and a second branch passes to the lung of the opposite side from the descending aorta, the first vessel evidently representing the pulmonary portion of the truncus (sixth aortic arch) and the second the patent arterial duct. This occurred in Dickson's[2] and Wirth's[3] cases, and also in that by Preisz.[4] In the latter, distinct traces of a partial development of the aortic septum were apparent. A common trunk provided with four semilunar cusps, 14 mm. in diameter, arose from the right ventricle above a large septal defect, and widened rapidly to 3 cm., becoming grooved externally to indicate the right and left portions of its lumen, that part on the right giving off the vessels of the arch, and thus representing the aorta, while that on the left yielded the vessels to the right lung and represented the pulmonary artery. An additional pulmonary artery was here also sent to the lungs from the descending aorta in the position of the ductus arteriosus.

In a few instances in which the defect in the aortic septum appears to be only partial, the common trunk divides immediately after its origin from the heart, two-thirds of its lumen on the right forming the aorta, and one-third on the left forming the pulmonary artery, which takes its normal course.

This early division occurs in both of Rokitansky's cases, and in them the partial character of the defect is also proved by the presence of a delicate sickle-shaped septum within the undivided portion of the trunk, joining its wall between the left and posterior semilunar cusps behind, and left and right cusps in front. In Clarke's[5] case the trunk divided early, but there was no sign of a rudimentary septum within.

The above are examples of true *persistent truncus arteriosus*. Under this title is also reported a series of cases in which the single trunk passing from the heart, represents the greatly dilated aorta or pulmonary artery, as the case may be, and an atresic cord attached to the external surface of the heart *represents the obliterated origin* of the other vessel. In one of Farre's cases, for instance, and in one by Forster, the single large trunk represented the pulmonary artery, and "a single coronary vessel which descended from the concavity of the arch to the base of the heart where it divided into two coronary arteries" was evidently the aorta, which was atresic at its origin, and was connected with the pulmonary by a large patent ductus. In Crisp's case, on the other hand, the pulmonary artery was rudimentary, and the large trunk represented the aorta.

As pointed out by Gierke, and also by Wirth, such cases should be clearly distinguished from the true persistent truncus due to complete absence of the aortic septum. Where the interventricular septum is

[1] *Trans. Path. Soc.*, London, 1864, xii, 62.
[2] *Jour. Anat. and Physiol.*, 1914, xlviii, p. 210.
[3] *Giessen Thesis*, 1912.
[4] *Ziegler's Beiträge*, 1890, vii, 247.
[5] *Trans. Path. Soc.*, London, 1885, xxvi, 178.

defective at its base, as it is in all these cases, there is a tendency for the aortic septum to develop irregularly, thus cutting off a narrow aorta or pulmonary artery, as the case may be, and the calibre of the smaller vessel is likely to become still further reduced in size by the passage of the bulk of the circulation into the larger trunk. For this reason obliteration of one trunk in biloculate heart where no interventricular septum is present, is a comparatively common event, and the cases should be sharply distinguished from a true defect of the aortic septum. Gierke suggests that the presence of four semilunar cusps such as occurred in Preisz's case is positive proof of an undivided primitive arterial trunk, while the presence of three semilunar cusps such as occurred in the McGill specimen, his own, Dickon's, and Wirth's argues that development of the aortic septum had occurred and that obliteration of one or other of the vessels had taken place as a secondary event.

Symptoms and Physical Signs.—Much the same remarks apply to persistent truncus as to bilocular heart, for symptoms and signs are not always commensurate with the seriousness of the lesion. But here the condition is a still graver one and the average duration of life is much shorter. Crisp's patient, a girl dumb from birth, with only slight cyanosis and clubbing, lived to twelve years, Forbes' to five years, Peacock's to thirteen months, and Buchanan's, who had a four-chambered heart with defect at the base of the septum, giving physical signs but no cyanosis, to six and a half months; all the others were marked cases of *morbus cæruleus* and died at birth or in early infancy. Vierordt quoted one dying at sixteen and another at nineteen years.

Communication between the Aorta and Pulmonary Artery.—(Partial Defect of the Aortic Septum.—A few cases have been described in which a circular or oval hole with perfectly smooth edges, and evidently not of inflammatory origin lies in the anterior wall of the aorta a short distance above the semilunar cusps, and leads directly into the pulmonary artery shortly above its origin. A valuable developmental study was made by Hektoen,[1] who gives a case of much interest and collected 9 others from the literature.

The effect produced upon the circulation by the abnormal communication between the two great vessels is the same as in a patent ductus arteriosus, but the two conditions are quite distinct and have an entirely different etiology. This lesion is not a patent ductus abnormally shortened so that aorta and pulmonary artery have been approximated, with an apparent hole as a result. It is a true defect, as is proved both by its situation, which is much nearer to the origin of both arteries than is the ductus, and by the fact that in several of the cases reported the ductus has been present as well. Neither is the defect of an inflammatory nature, as is well seen in the smooth condition of its edges in the cases of Girard, Wilks, and Rickards, and from the character of the combined defects in the latter and in Fraentzel's case.

The abnormal opening is clearly a partial defect of the aortic septum, not at its junction with the interventricular septum, but higher up in

[1] *Trans. Chicago Path. Soc.*, 1905.

its own substance, probably at the point where the distal bulbar swellings meet the aortic septum proper in the embryo.

In all the recorded cases but one, the hole lay in the aortic wall a short distance above the semilunar cusps. In that of Rickards the aortic valve was bicuspid, and its segments congenitally fused. A funnel-shaped opening communicated with the pulmonary artery and lay behind the larger (fused) cusp. A triangular defect in the interventricular septum existed also in this case.

Instead of opening into the pulmonary artery, the hole may lead from the aorta into the right ventricle as in the cases of Livingstone[1] and Cayla. In one of Hektoen's cases the anomalous opening led from the aorta into the right ventricle through a defect at the base of one of the semilunar valves. This, also, is a most interesting example of a defect of the lower (bulbar) part of the aortic septum.

A *communication* between the aorta and pulmonary artery *of an acquired nature* may occur in much the same situation as in the congenital form in aneurism of the base of the aorta. There is quite a large series of cases, especially in the earlier literature, which is reviewed by Brocq.[2] The congenital cases are to be distinguished from those due to perforation of an aneurismal sac by the smooth appearance of the edges of the opening and the healthy arterial wall. The physical signs produced are the same and are often of remarkable intensity. Gairdner[3] reported a typical case, characterized by a continuous murmur.

The pulmonary artery was larger than the aorta in Wilks' and Rickard's cases, a little smaller in Fraentzel's and Girard's cases. Marked hypertrophy and dilatation of all the chambers of the heart, especially of the right ventricle, constantly results. In Girard's and Rickards' cases, in which there was no other cardiac lesion, the hearts weighed, respectively, 670 gms. and 23 oz. (651.8 gm.).

Symptoms and Physical Signs.—Cyanosis is not, as a rule, present, and there is no characteristic picture, excepting that obstruction to the circulation is clearly manifest. All the cases recorded died before middle life with anasarca and other symptoms of chronic heart disease; those of Girard, Rickards, and Fraentzel reached thirty-seven, thirty, and twenty-five years respectively. Wilks' infant died at eight months, Hektoen's and Lebederber's at birth. Precordial discomfort, amounting often to actual distress, was present since childhood in Rickards' patient, as also in Fraentzel's and Girard's, and in the two latter there was dyspnœa on exertion and slight cyanosis. Physical signs may be absent or may be very marked, and they may vary, being sometimes quite atypical, or sometimes those usually associated with a patent ductus arteriosus. Owing to the great hypertrophy of the heart the cardiac dulness is usually much increased, especially to the right, and there is precordial bulging. Girard's case was characterized by a slight thrill and systolic murmur at the apex, which latter gave place later to reduplication of the first sound and distinct gallop rhythm.

[1] *New York Med. Rec.*, 1883, p. 249.
[2] *Revue de méd.*, 1885, v, 1046 and 1886; vi, 786.
[3] *Glasgow Hospital Reports*, 1899.

A diastolic murmur is common. In Rickards' case the cardiac dulness was enormously increased, and there was an intense purring double thrill over the cardia, and murmurs, systolic and diastolic, running into each other, were heard over the whole front and back of the chest, so loud as to be audible even through the bedclothes. In Fraentzel's patient, in whom there was a gaping opening 12 mm. across between the two vessels, and the right pulmonary artery arose from the ascending aorta, the heart was found to be greatly enlarged; both sounds were heard at all the ostia, and a systolic murmur was heard at the apex; in the fourth left space near the sternal border was a loud systolic and a long diastolic murmur, the latter heard with equal intensity over the base of the xiphoid cartilage. Both sounds and a diastolic murmur were audible in both second spaces, the murmur being louder and rougher in the second right space than in the left. Both sounds as well as systolic and diastolic murmurs were audible in the carotids.

DEVIATION OF THE AORTIC SEPTUM.

According to the teaching of Rokitansky, transposition of the arterial trunks, *Rechtslage* or deviation to the right of the aorta, as well as certain developmental forms of pulmonary and aortic stenosis, are due to irregularities in the development of the septum within the aortic bulb, or to its malunion with the interventricular septum. As this theory with certain modifications still finds general acceptance, the cases embraced by it will be considered here.

Transposition of the Arterial Trunks.—This may be defined as an alteration in the position of the two great vessels relative to the ventricles of the heart or to each other at their origin, so that they either spring from reversed ventricles, the aorta from the right and the pulmonary from the left chamber (complete transposition), or from the ventricle to which they normally belong, but in a reversed relationship ("corrected" transposition).

The condition was first described by Baillie in 1797, and early cases were reported by Farre in 1814, Ward[1] in 1851, Peacock[2] in 1854, Buchanan[3] and Meyer[4] in 1857, Cockle[5] in 1863, and Kelley[6] in 1870. As a result of systematic observation of the autopsy material of infants at the St. Petersburg Foundling Hospital, Thérémin found 26 cases of transposition among 106 cardiac defects. In his summary of the literature in 1898, Vierordt mentions (p. 47) 76 cases of transposition among 383 cardiac defects analyzed. Some thirty additional cases have been reported since. Among 270 cardiac defects in the London Museums examined by Keith, transposition occurred in twenty-five. In our series of defects it was present seventy times.

Pathogenesis.—Peacock and others ascribed this anomaly to an irregularity in the development of the aortic septum, but until Rokitansky's

[1] *Trans. Path. Soc.*, London, 1851, v, 67.
[2] *Ibid.*, 1854, vi, 117.
[3] *Ibid.*, 1857, viii, 149.
[4] *Virchows Arch.*, 1857, xii, 364.
[5] *Medico-Chir. Trans.*, 1863, xlvi, 193.
[6] *Trans. Path. Soc.*, London, 1871, xxii, 92.

work appeared in 1875, it remained a little understood phenomenon. In some minor particulars the observations of Rokitansky upon development do not coincide with those of later observers, but it is in the elucidation of the complex and hitherto obscure subject of transposition of the arterial trunks that the value of his great achievement may be said chiefly to lie. Rokitansky's explanation of transposition is one of those revelations, astonishing by its simplicity, and, as Vierordt remarks, he had the singular triumph of having supplied a working hypothesis that has not only explained the facts of his own experience, but has outlined and foreseen other pathological possibilities which have since been realized. He described and figured sixteen different forms of transposition, due, he believed, to different degrees and combinations of deviation or malunion of the aortic and interventricular septa, some of which he himself observed, and others have since been recorded by later workers. Even if the advance of comparative embryology should unfold some other explanation of this subject, the verification of Rokitansky's brilliant hypothesis by the subsequent observation of different forms of transposition shown by it to be possible, indicates that, so far as it goes, his theory is true, and that growing knowledge will amplify rather than supersede his solution of this difficult problem.

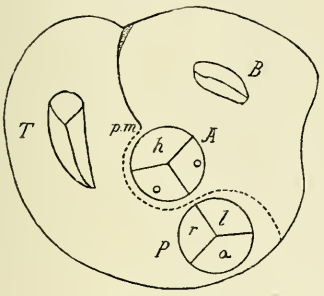
Since the above statement was written for the first edition of this work, a remarkably clear exposition of Rokitansky's theory in the light of recent investigations upon the normal anatomy of the bulbus cordis in the dipnoan and reptilian heart and in the mammalian embryo, has been published by Jane Robertson.[1] The following is a brief statement of Rokitansky's doctrine of transposition, as corroborated and amplified by the result of these researches.

As may be seen by a glance at the normal adult heart, the great trunks normally undergo a distinct torsion upon each other just above their origin, so that the pulmonary artery, which arises in front and to the left, passes back behind the ascending aorta to the lungs, while the aorta, although coming to lie ventral to the pulmonary artery, springs from the heart behind it and to the right. This torsion of the vessels is represented in the bulbus cordis of the early embryo and in the dipnoan fish by a spiral arrangement of the valvular endocardial folds of the bulbus cordis, which results from a kinking upon itself of the bulbus, which structure was at an earlier stage a straight tube. The aortic septum is formed in its proximal portion by fusion of the spirally placed endocardial ridges of the bulbus cordis, and in its distal part by a growth downward of a septum in the common arterial trunk. If for any reason this normal kinking does not occur and the bulbus remains a straight tube, the aortic septum will not assume its spiral form, and the normal torsion of the great trunks upon each other cannot take place. The result is an aorta arising anteriorly and passing directly upward to the arch, and a pulmonary artery arising posteriorly and passing directly backward to the lungs, *i. e., transposition.* In other words, transposition of the arterial trunks is due to a lack of development of the torsion that normally

[1] *Jour. Path. and Bacteriol.*, 1913, xviii, 191.

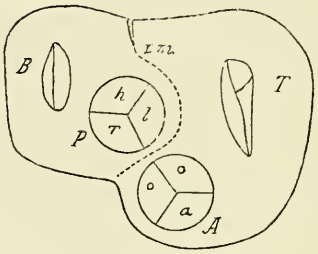
occurs. The transposed vessels may be placed in their proper ventricles in spite of their relative displacement, by the sympathetic adjustment of the aortic in its union with the interventricular septum. In this case the transposition is "corrected" (Rokitansky's Scheme A). Or the transposed vessels may be placed in the *reversed* ventricles by the union of the interventricular with the proximal portion of the malposed aortic septum, when "*uncorrected*" (*anomalous*) *transposition* results (Rokitansky's Scheme B).

Fig 32



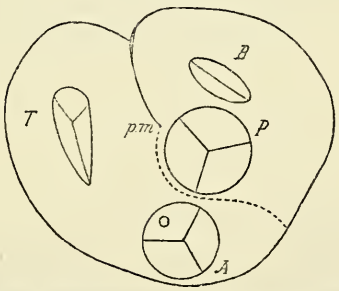
Normal relation.

Fig. 33



Corrected transposition.

Fig. 34



True complete transposition, vessels in reversed ventricles.

A, aorta; *P*, pulmonary artery; *T*, tricuspid valve; *B*, bicuspid valve; *pm*, pars membranacea; *p*, posterior cusp; *a*, anterior cusp; *lr*, left, right cusps (the small circles indicate the situation of the coronary article.) (Republished from Vierordt, Nothnagel's System, 1898, xv, 1, 2.)

Rokitansky recognized this spiral disposition of the aortic septum and taught that these two factors, a deviation of the septum within the aortic bulb and its faulty union with the interventricular septum, might occur in all degrees and combinations, giving rise to a corresponding number of different forms of displacement of the arterial trunks or of "*corrections*" of such displacements. He distinguished two main classes (according as the transposition is "*corrected*" or otherwise by the interventricular septum), with eight sub-varieties in each. Of these his "Scheme A" has as its type or starting point the normal relation, in which the concavity of the septum looks backward and to the right. The different subvarieties are constituted by the different degrees of

deviation of the aortic septum rotating in an imaginary circle from right to left. The characteristic of the group as a whole is that the interventricular unites with the aortic septum in such a way that, although the trunks are altered in their relation to each other, they remain placed in their respective ventricles: that is to say, the transposition is "*corrected.*"

In his second group, or "Schema B," on the other hand, the arteries arise throughout from the "reversed" ventricles; that is to say, the transposition is "*uncorrected*" in the union of the interventricular septum. The type, or fundamental form from which the series starts, is the so-called *transpositio vera,* in which the septum has rotated through 180 degrees, so that its concavity looks downward and to the left, and the arteries lie in reversed cavities in the exact opposite of the normal position, the aorta to the left and anteriorly, the pulmonary to the right and posteriorly (Fig. 34). Another explanation of transposition has been offered recently by Keith, namely, that it is due to an atrophy of the bulbus cordis around the pulmonary artery, and its great muscular development about the origin of the aorta, where it normally undergoes involution. The effect would be the pulling round of the aorta at its orifice to the position normally occupied by the pulmonary artery, so that the relation of the two vessels to the auricular canal becomes reversed.

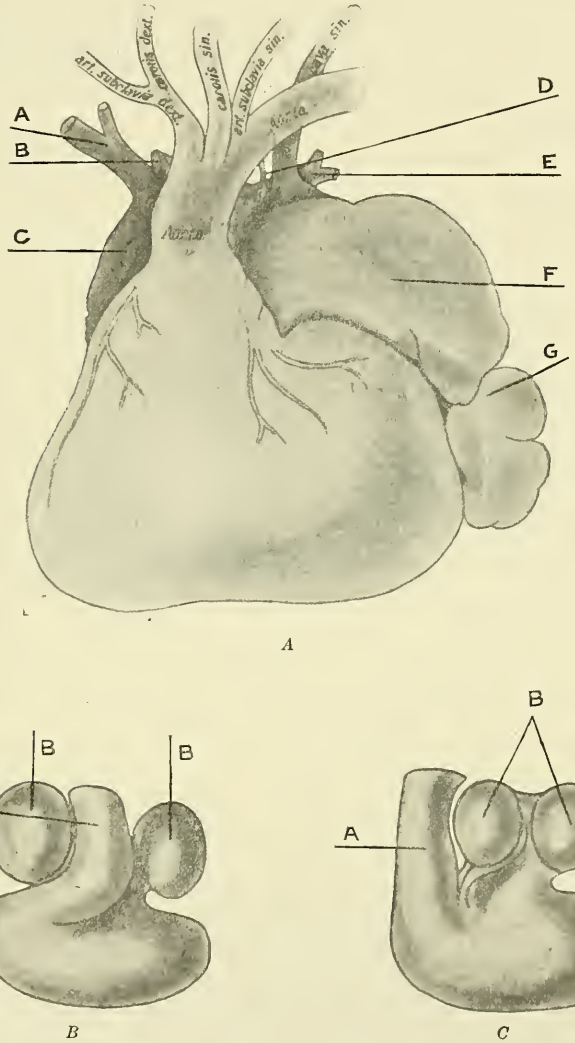
A similar result would be attained by supposing a reversal of the normal right to left bulboventricular bend, so that this undergoes a left to right twist, which would bring the vessel lying posteriorly into relation with the right side of the auricular canal. Such a reversal of the bulboventricular bend has been suggested to me by Dr. Lewis as a probable explanation of those cases of transposition in which the transposed aorta is cut off by an anomalous septum from a common ventricle, and has also been mentioned in this connection by Keith.

From a consideration of the above theories, and from the study of two models made by Dr. Frederic Lewis and myself, the series of events occurring in transposition appears to us to be as follows: (1) A reversal of the bulboventricular bend, so that the two great trunks resulting from division of its distal aortic portion come to occupy a reversed relation to the auricular canal; (2) a reversal of the normal kinking of the aortic bulb so that it remains a straight tube or assumes a curve complementary to the reversed bulboventricular twist below; (3) a consequent reversal of the normal spiral arrangement of the bulbar endocardial ridges; and (4) a resulting malposition of the aortic septum so that its spiral twisting either does not take place, or takes place in a reversed direction, leading to a lack of the normal torsion of the great arterial trunks, that is, *transposition.*

The interdependence of the first and second of the above events is evident from a glance at the compensatory curves of the normal embryonic bulbus (Plate V), but the question as to which of these two is of primary occurrence is not altogether clear. The reversal of the bulboventricular twist may be of the nature of a localized *situs inversus* and the causative factor of the whole proceeding. Or it may be secondary to a primary arrest of the kinking that normally takes place in the aortic bulbus, and of the consequent lack of spiral disposition of its valves.

That the second of these two alternatives, namely, a primary arrest of development, may be the correct solution is suggested in a striking

FIG. 35



A

B *C*

A, Wenner's case of cor biatriatrum triloculare with transposed aorta and pulmonary artery passing up to the right, and both right and left auricular appendages displaced to the left side. *A*, Superior vena cava; *B*, right pulmonary artery; *C*, right auricle; *D*, ductus botalli; *E*, left pulmonary artery; *F*, right auricular appendix; *G*, left auricular appendix.

B, figure of normal embryonic heart showing the position which the truncus comes to occupy between the auricular appendages after the normal shunting to the left of this structure has taken place. *A*, common arterial trunk; *B*, *B*, auricular appendages.

C, figure of embryonic heart in which the normal shunting to the left of the common arterial trunk has not occurred, so that this structure still comes off entirely from the right side of the heart (as in the very early stages), and both auricular appendages still lie on the left (as in Wenner's case). *A*, common arterial trunk; *B*, auricular appendages. From *Beiträge zur Lehre der Herzmissbildungen*, Case 9. Otto Wenner, *Virch. Arch.*, 1909, 196, pp 140, 155.

way by two remarkable cases reported by Wenner,[1] and Birmingham[2] of "pure"dextrocardia, in which the transposed vessels arose from the extreme right side of a common (in Birmingham's case of a right) ventricle, and *both auricular appendages lay entirely on their left side*, just as in the very early embryo, the common auricle lies to the left of the common trunk. In both cases the dextrocardia was not a true situs inversus, but the apex of the heart was formed by the right ventricle, again evidencing a persistence of an early embryonic state, and a true primary arrest of development.

Pathology.—It is impossible to follow Rokitansky's minute classification in a statistical study of recorded cases, for the relation of the vessels to each other is often indefinitely stated. For practical purposes the classification into complete, corrected, and partial transposition, suggested by Vierordt, may be used.

(*a*) In *complete transposition*, the vessels arise from reversed ventricles. This occurred in 43 of our 70 cases. In 18 of these the aorta arose from the right ventricle to the right and in front, and the pulmonary artery to the left and behind. The so-called *transpositio vera*, in which the aorta arises in exactly reversed relation to the left and anteriorly, and the pulmonary artery from the left ventricle to the right and posteriorly, is illustrated by the cases of Pye-Smith[3] and Thiele. The pulmonary rose above a defect in the septum and the aorta from the infundibulum of the right ventricle in three of Thérémin's cases, and in those of Lees and Rheiner. The aorta rose from both ventricles above the defect, the pulmonary from the left ventricle, in that by Buchanan.[4]

(*b*) In *corrected* transposition (see Fig. 33 Scheme A). the relation of the vessels to each other is altered, but they are placed in their proper ventricles by the union of the interventricular septum. Minor degrees of displacement probably often pass unnoticed, for the "correction" prevents pathological results. More extreme grades can be at once recognized. Six almost identical cases are described by Rokitansky (two cases), Rauchfuss, Tonnies,[5] and Thérémin (two cases), in which the aorta and pulmonary artery are completely reversed in relation to each other, but arise each from their own ventricle. In all there was a defect in the interventricular septum at the base, and in all *the auriculo-ventricular orifices were also transposed*, the mitral lying in the right, the tricuspid in the left ventricle, and thus the "correction" of the transposition of the arteries by the septum was seemingly nullified; the aorta arises from a ventricle of venous form (in that it has a tricuspid valve), the pulmonary from an arterially constructed one. Rokitansky suggests that in these cases "the ventricle in which the septum arises anteriorly forms as the arterial one." Fingerhuth described a case of corrected transposition with situs inversus of the viscera, and no transposition of the ventricles.

[1] *Virchows. Arch.*, 1909, cxcvi, 127.
[2] *Jour. Anat. and Physiol.*, 1893, xxvii, 139.
[3] *Trans. Path. Soc.*, London, 1873, xxiii, 80.
[4] *Ibid.*, 1857, viii, 149.
[5] *Göttingen Thesis*, 1884.

(*c*) *Partial transposition,* in which both vessels arise from the same ventricle or from a common ventricle in reversed relations, is relatively infrequent. *Both vessels may arise from the right ventricle,* as in Thérémin's forty-first observation and in Tooth's case,[1] in which a large thick-walled aorta arose from the usual origin of the pulmonary artery, which was itself small, thin-walled, bicuspid, and was given off from the right ventricle directly behind the aorta. *Both vessels may spring from the left ventricle.* Thus, Crocker reported a girl, aged thirteen years, in whom the pulmonary artery, small and constricted, arose from a small, thick-walled, left ventricle to the right and anteriorly, while the aorta arose from the same cavity posteriorly, and communicated with the right ventricle through a defect in the septum. *Both vessels may arise transposed from a common ventricle,* as in two examples of cor biatriatrum triloculare with pulmonary atresia and transposition, and in the biloculate heart reported by Rudolf. The remarkable cases of displacement of both auricular appendages to the left of the transposed vessels fall in this category. Finally, the transposed vessels may arise from a rudimentary cavity cut off by an anomalous septum from the common ventricle.

The condition of the semilunar cusps in transposition is of interest. In one or other of the vessels, more commonly in the pulmonary, they are frequently deformed, of unequal length, bicuspid, or, as in Bokay's case, markedly increased in depth. Their position varies with the degree of displacement, and should therefore be carefully observed, as the degree of deviation may be thus detected. In true transposition, for instance, the non-coronary cusp in the aorta lies anteriorly instead of posteriorly.

Changes in the relative size and thickness of the two great trunks are usually present, and are of importance as supporting Rokitansky's view that an altered position of the aortic septum is a fundamental part of the condition. In spite of the fact that the pulmonary arises from the left ventricle, which is anatomically constructed as the strongest of the two chambers, this vessel is usually thin-walled and narrowed and its orifice is stenosed or atresic, while the aorta is dilated. Among Rokitansky's 18 cases of transposition, pulmonary stenosis or atresia occurred 11 times, and it was present in 17 out of the 25 cases of Keith's series. In a few instances the reverse holds good and a large thick-walled pulmonary may be combined with a short, narrow aorta. Thérémin's series of 14 cases in infants, 10 of which were of complete and 4 of partial transposition, forms a remarkable exception to the above statement. In 3 of his cases the pulmonary was dilated, and in the remainder it was equal in size to the aorta. In our own series, which includes these 14 of Thérémin's, among 70 cases, in 43 of which the transposition was complete, in 22 partial, and in 5 "corrected," the pulmonary was stenosed or atresic in 23 cases.

The Fetal Passages.—In complete transposition the venous blood from the right heart is distributed to the arterial system through the aorta, while the aërated blood entering the left auricle is returned again

[1] *Trans. Path. Soc.,* London, 1879, xxxi, 92.

to the lungs by the pulmonary artery. The conditions of the circulation are thus of the poorest, and unless one or other of the fetal passages remains open, life cannot be sustained. The interventricular septum is frequently entire, but a widely patent foramen ovale is nearly always present and combines with a patent ductus or with a septal defect to allow of the passage into the aorta of the aërated blood. Very rarely does one of these conditions exist singly. In our series, among 37 cases of complete transposition the foramen ovale was patent 32 and the ductus arteriosus 22 times. A patent foramen was the only communication between the two sides of the heart in 8 cases, namely, those by Emanuel, Dorning,[1] Kelly, Cockle, Bokay, and in three of Thérémin's cases. It was combined with a patent ductus in 14 cases, with a defect of the interventricular septum in 6, and with patency of both of these openings in 4 cases. The ventricular septum was completely closed in 25 cases and was defective in 12, in one of which, that by Heuyer and Campergne,[2] the septal defect was the only communication, and in another by Guttmann[3] the ductus arteriosus was also patent. In Thérémin's thirty-seventh observation and in Ramm's case, a large patent ductus was the only communication between the right and left heart. In a few cases the bronchial arteries were markedly dilated.

Bokay[4] has made an analysis of 43 cases of complete transposition, with regard to the condition of the fetal passages, and there are 33 additional cases in our series from the literature. The following table shows the condition of the fetal passages in these 76 cases.

	F. O. Patent.	D. A. Patent.	V S. Defect.
F. O. patent	16	36	7
D. A. patent	36	3	3
V. S. defect	7	3	5
Patent F. O., defect V. S., patent D. A.	4	4	4
Total	63	46	19

The abbreviations are as follows: F. O., foramen ovale; D. A., ductus arteriosus; V. S., interventricular septum.

Hypertrophy and Dilatation of the Heart.—Under the altered conditions of the circulation the aorta is required to supply blood, not only to the systemic circulation, but through one or other of the persistent fetal passages to the lung. The right heart is practically invariably hypertrophied and dilated, sometimes to an enormous extent, and the right auricle likewise. The left chambers usually share in these changes though to a less degree.

Symptoms and Physical Signs.—During the period of fetal circulation, transposition of the vessels is of little pathological significance, so that, unless associated anomalies exist, the subjects are born at full term, well developed, and apparently normal. In complete transposition, marked

[1] *Trans. Am. Ped. Soc.*, 1891, ii, 46.
[2] *Bull. de la Soc. Anat.*, April, 1913, p. 209.
[3] *Deut. med Woch.*, 1893, xc, 74.
[4] *Arch. f. Kinderheilk.*, 1911, lv, 321.

cyanosis is almost always a prominent feature, but it may not be present at birth, appearing usually after some days or weeks, and perhaps developing, as Thérémin suggests, as the ductus becomes obliterated. On account of the extreme degree of the cyanosis, clubbing of the fingers and toes usually develops in infants which have survived the first six months of life. In partial transposition, on the other hand, or in complete transposition with large septal defects, cyanosis may be quite moderate in degree. In Thérémin's patient, dying at three and a half years, there was no cyanosis until the last illness, but large defects of interauricular and interventricular septa combined to relieve the situation. In a remarkable case of partial transposition, recorded by Lebert,[1] death occurred from failing compensation, at the age of twenty, without any sign of cyanosis having developed during life. The patient was a young man in good health until three years previously, when cardiac symptoms developed suddenly after lifting a heavy weight. The aorta arose in front of the pulmonary from the right ventricle, the pulmonary was stenosed and a large septal defect admitted the index finger.

In uncomplicated cases, and where a ventricular septal defect is either not present or is of small size, *physical examination may yield no evidence of the defect*, except a sharply accentuated second sound over the pulmonary (aortic) area. The combination of marked cyanosis with signs of hypertrophy of the right heart and an entire absence of adventitious sounds, or precordial thrill, in an infant or young child, is strongly suggestive of transposition, and a successful diagnosis has frequently been made on these features. In Thérémin's thirtieth observation this was based upon "cyanosis increasing when the infant cried, hypertrophy of the heart both in vertical and transverse diameter, the heart sounds loud and accentuated but pure, the aortic and pulmonary sounds distinct." In Ramm's case, aged fifty-six days, a probable diagnosis was made. Here also there was cyanosis from birth, no murmur, no accentuation or reduplication of the heart sounds, but dulness extending beyond the right sternal border and upward to the second rib, of so marked a character that a mediastinal tumor was at first suspected. In Thérémin's thirtieth, thirty-first, thirty-eight, and thirty-ninth observations the heart sounds were free from murmurs, although muffled, and cardiac dulness was increased to the right. On the other hand, a loud systolic murmur with maximum intensity at the apex was heard in Kelley's case, the same at the base and at the back in Pye-Smith's, and was probably produced by the patent foramen ovale present.

The patent ductus, patent foramen, or septal defect present, may produce their characteristic physical signs, and thus obscure the negative character of the auscultatory phenomena, which is significant of the clinical picture of an uncomplicated transposition.

Prognosis.—The duration of life varies in the three groups distinguished. In complete transposition it is usually very short. In 32 of the 40 cases in our series it varied between eleven months and a few days. When a septal defect is present, life may be considerably prolonged; the age of

[1] *Virchows Arch.*, 1863, lxxxii, 405.

sixteen years was attained by Keith's patient, eleven by Emanuel's, and four by Buchanan's. In partial or corrected transposition on the other hand, early adult life is usually reached. Birmingham's patient was twenty, Tonnies' twenty-one, Elliott's[1] nineteen, Young's thirty-six, and Geipel's forty-six years. Vierordt gives the following analysis of the duration of life in 75 cases. To this is added that of the 70 in our series, of which there were 57 classified as the primary lesion, and 13 complicating other defects.

Duration of Life in Transposition

Age.	Cases in this series. Complete	Partial.	Corrected.	Total.	Vierordt's cases.
Born dead	0	0	0	0	3
1 to 24 hours	0	0	0	0	1
1 to 7 days	0	0	0	0	7
7 to 14 "	7	2	0	9	5
14 to 30 "	3	2	0	5	7
1 to 2 months	8	0	0	8	14
2 to 6 "	7	2	2	11	12
6 to 12 "	7	1	0	8	9
1 to 2 years	1	2	0	3	2
2 to 5 "	6	0	0	6	6
5 to 10 "	1	2	0	3	0
10 to 11 "	1	1	0	2	3
11 to 21 "	1	6	0	7	0
21 to 30 "	1	0	0	1	5
30 to 40 "	0	2	2	4	1
40 to 50 "	0	0	1	1	0
Age unmentioned	0	2	0	2	0
Total	43	22	5	70	75

PULMONARY STENOSIS AND ATRESIA.

Pulmonary stenosis is the form of cardiac defect most familiar to the practitioner. It is of much clinical importance on account of its comparative frequency, the relatively long duration of life, and the prominence of the cyanosis nearly always associated. To the student also it is a subject of the highest interest, for in its symptomatology and pathogenesis are focused the most difficult problems of congenital cardiac disease.

Owing to the wide variations in the conditions presented and the differing aspects from which the subject must be approached, a classification of the different forms is as difficult as it is necessary. Rauchfuss points out that the simple anatomical findings furnish the best guide to a useful grouping. Thus, the *degree of narrowing* is important, and a simple stenosis is to be distinguished from a complete atresia; from the stand-point of pathogenesis, the *seat and character of the stenosis* are criteria of much value; and thirdly, the *presence or absence of defects of the interventricular septum* provides a dividing line of the greatest importance. This last is important etiologically as indicating the stage of embryonic or fetal life at which the stenosis took place, and clinically in that the duration of life and symptomatology differ somewhat in the two groups.

[1] *Jour. Anat. and Physiol.*, 1877, xi, 302.

Statistics.—Pulmonary stenosis is probably the commonest of all cardiac anomalies. The cases are scattered so freely through the literature that an exact statistical statement is impossible. Vierordt estimated at least 300 in 1898, and placed coarctation of the aorta next in frequency with 130 cases. Among 181 anomalies of the heart which he analyzed, Peacock found 119 of pulmonary defect. In 1906 Keith[1] examined 185 specimens of cardiac malformations in the hospital museums of London, and found that in 135, or 70 per cent., there was an anomalous condition of the pulmonary tract, the deformity being in the conus of the right ventricle in 133 cases and in the pulmonary valve in 22. In his later communication,[2] among 272 malformed hearts examined in the various London Museums, Keith found 141 in which the defect was due to an imperfect transformation of the bulbus cordis of the embryo. Of these 141, in 19, there was incomplete fusion of the infundibulum with the body of the right ventricle (conus a separate chamber); in 44, partial arrest in development of the infundibulum; in 37, complete arrest of the infundibulum; in 23 fusion of semilunar valves; in 7, partial or complete absence of the body of the right ventricle with development of the infundibulum; in 4 subaortic stenosis; and in 7, congenital aortic stenosis.

Among the cases of anomalies analyzed here, there are 150 of congenital pulmonary disease. The proportion of stenosis to atresia in recorded cases analyzed is as follows:

	Stenosis.	Atresia.	Number analyzed.
Kussmaul	64	26	90
Rauchfuss	81	33	114
Peacock	90	29	119
Vierordt	83	24	107
Thérémin	20	10	30
This series	116	34	150

The relatively high percentage of atresia in Thérémin's cases is explained by the fact that his material was entirely among infants, in whom the mortality from atresia is high.

The condition of the fetal passages was the subject of statistical study by Meyer, Kussmaul, Taruffi, and other authors, of whose work a full review is given by Vierordt. A defect of the interventricular septum exists in the great majority. The number of cases with closed septum is relatively larger in atresia than in stenosis; thus Rauchfuss finds among 192 cases, 171 in which the interventricular septum is defective and 21 in which it is closed. Of these 21, 10 are cases of atresia and 11 of stenosis. Among Vierordt's 83 cases of stenosis are 71 with defective and 12 with closed interventricular septum; among his 24 of atresia, in 14 the septum was defective and in 10 it was closed. When the interventricular septum is entire, the foramen ovale is usually widely patent, but it also may in rare cases be closed.

Among the 116 cases of stenosis analyzed here the interventricular septum was defective in 95, and entire in 21 cases. In 12 of these 21

[1] *Festschrift, Quatercentenary Aberdeen University*, July, 1906.
[2] *Hunterian Lectures, Lancet*, 1909, ii, 359, 433, 519.

the foramen ovale was patent, but in 9 the auricular septum was also closed, and no communication existed between the two sides of the heart. Among the 34 cases of atresia the interventricular septum was defective in 26 and entire in 8 cases. Of these 8, in one the foramen ovale was also closed but there was a large patent ductus. The ductus arteriosus is nearly always patent in atresia but is usually closed in stenosis. Among the 82 cases of pulmonary stenosis classed as the primary lesion in the chart, the ductus was patent in only 11; of the 24 cases of atresia, it was patent in 15 cases. The condition of the cardiac septa and ductus in these cases was as follows:

	Stenosis.		Atresia.	
	Number analyzed.	Number with patent D. A.	Number analyzed.	Number with patent D. A.
F. O. and V. S. closed	7	0	1	1
F. O. patent, V. S. closed	11	1	5	4
F. O. closed, defect V. S.	40	5	7	3
F. O. patent, defect V. S.	24	5	11	7
Total	82	11	24	15

Rechtslage of the aorta is present in the majority of cases with septal defect, and is especially frequent in atresia. Among the 64 cases of pulmonary stenosis with septal defect, classified in the chart as the primary lesion, it was present in 39 cases, in 29 of which the aorta arose from both ventricles above the defect, and in 10 chiefly or entirely from the right ventricle. Among the 18 cases of atresia with septal defect the aorta arose from both ventricles above the defect in 5, entirely from the right ventricle in 10.

Pathology.—Pulmonary Stenosis.—The narrowing may involve the whole pulmonary tract, or be localized to the valve, artery, or conus. Two distinct types may be recognized:

1. In a few cases the stenosis is valvular in character and is produced by a thickening, shortening, or fusion of the pulmonary cusps. A thick diaphragm with three raphe of fusion on its arterial surface is usually formed, which protrudes into the pulmonary artery in a funnel-shaped way and is perforated by a circular or triangular opening of varying size. The pulmonary artery is frequently dilated above, may be normal, or somewhat thin-walled. The conus below the valve shares in the hypertrophy of the right ventricle, but is otherwise normal; the interventricular septum is usually closed. There is every evidence to show that the stenosis has originated in an inflammatory process in later fetal life after the heart has been fully formed.

2. In the second and larger group, the cusps may or may not be thickened or fused, but the stenosis is due to a rudimentary condition, hypoplasia, or deformity of some part of the pulmonary tract. In these cases a defect of the interventricular septum is usually associated and a deviation to the right of the aorta, so that this arises from both ventricles above the defect, or chiefly from the right ventricle, communicating with the left through the defect. Such forms, which suggest a developmental origin, make up the great majority of cases of pulmonary stenosis, and the combination of these three conditions, pulmonary

stenosis, defect of the septum at the base, and *rechtslage* of the aorta, is probably the commonest of all cardiac anomalies.

In the majority of cases—in Keith's estimate 90 per cent.—the conus of the right ventricle is involved in the deformity. Two distinct types of conus stenosis may be distinguished. The whole infundibulum may be more or less constricted, its musculature thickened, and the endocardium opaque. In a case of this kind, reported by Cautley,[1] the pulmonary cusps were delicate and healthy above the stenosis, but both they and the artery were very small. Usually the valves are thickened, fused, or rudimentary, and they are often bicuspid. Sometimes a thin diaphragm with delicate raphe showing no sign of inflammatory change, is stretched across the pulmonary orifice, suggesting an incomplete division of the endocardial cushions. In these cases a defect of the septum is almost invariably present.

A second group of conus deformities is that in which a cavity, described by some of the older pathologists as a third ventricle, is cut off from the sinus of the right ventricle by a definite septum perforated by a small opening. There are 19 in this series, including one case of atresia. Keith describes and figures an illustration of this anomaly. The infundibulum is enormously dilated and communicates with the sinus by a small opening with thickened fibrous borders. The pulmonary cusps are large and competent, the artery dilated above, and there is a small defect of the interventricular septum. Another variation of this form of conus deformity is figured by Andrewes.[2] The conus is atrophied and is represented by a small cavity with thick muscular walls. It communicates with the sinus of the ventricle by an opening admitting a crow-quill one-quarter inch below the pulmonary cusps, which are small, bicuspid, and not thickened.

Hypertrophy and dilatation of the right ventricle and auricle are constant in pulmonary stenosis, and in the cases associated with defect of the septum at the base and *rechtslage* of the aorta. In these the hypertrophy is sometimes most marked in the wall of the sinus of the ventricle, indicating that it had been produced by the force needed to send the blood into the aorta through the defect, rather than by the obstruction in the pulmonary artery. The aorta is usually thick walled and of large caliber. In the developmental cases the pulmonary artery is usually narrow and thin-walled, resembling a vein in structure. When the stenosis is confined to the valve, the artery may be dilated.

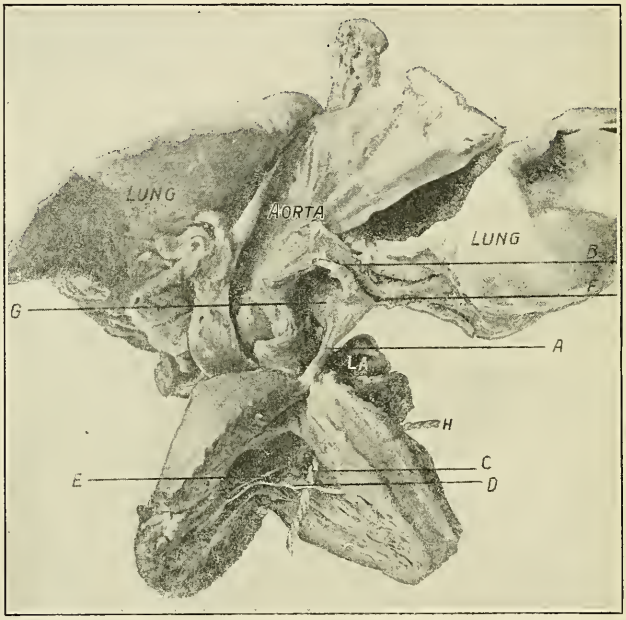
Pulmonary Atresia.—All that has been said of the seat and character of the deformity in pulmonary stenosis applies equally to a complete atresia. In a small series of cases the point of obliteration is at the valve, the artery dilated above, the foramen ovale widely open, and the septum entire. In Weiss'[3] case the seat of atresia was in the conus, which admitted only a pinhead or a fine straw, and was lined by thickened endocardium; just above this were two fairly large pulmonary cusps, and the artery itself was comparatively large. There was a small patent foramen ovale,

[1] *Edin. Med. Jour.*, 1902, xii, 257.
[2] *Trans. Path. Soc.*, 1865, xvii, 45.
[3] *Brit. Med. Jour.*, 1877, ii, 378.

a large defect of the septum at the base, and a large thick-walled aorta arose from the right ventricle above the defect.

The pulmonary artery may be obliterated for some distance above the valve, forming a fibrous cord, which may emerge suddenly from the fleshy outer wall of the ventricle and give no sign of its origin from within, or it may be patent throughout, diminishing toward the orifice in a funnel-shaped way. In such cases the cusps may be seen thickened and fused with each other at the bottom of the cul-de-sac formed by the artery, or they may form a triradiate elevation of three fleshy cushions; or no trace of them may remain. The aorta is usually very large. When a defect in the septum is present it rides over it, or in many cases arises entirely from the right ventricle.

Fig. 36



Heart and lungs of an infant, cyanotic from birth, showing (*A*) atresia of the pulmonary artery; *B*, patent ductus arteriosus supplying lungs; *C*, defect of interventricular septum at pars membranacea, guarded by (*D*) an anomalous valve with false chordæ tendineæ; *E*, tricuspid orifice; *F*, left pulmonary artery; *G*, right pulmonary artery; *H*, cord passing through the septal defect; *LA*, left auricle. (From a specimen in the McGill Pathological Museum, presented by Sir William Osler.)

The foramen ovale is frequently widely patent. It may be the only means of communication between the two sides of the heart, the interventricular septum remaining entire. Such cases are less frequent, and the condition is more serious than that associated with septal defect.

The alterations in the cavities of the heart vary with the condition of the interventricular septum. When this is entire the left ventricle is greatly hypertrophied and dilated, and both auricles share in the enlargement, while the right ventricle undergoes a true concentric hypertrophy, its wall becoming greatly thickened and its cavity aplastic and

lined with opaque thickened endocardium, or in some instances completely obliterated. When a defect of the septum exists, the right ventricle is greatly hypertrophied and is dilated as well, and the right auricle is correspondingly enlarged, the left chambers remaining relatively small. When the aorta rides over the defect in the septum, the left ventricle may share in the hypertrophy.

The Pulmonary Circulation.—When the pulmonary artery is obliterated the blood supply usually reaches the lungs through the widely patent ductus, but this is sometimes closed or absent. Meckel first suggested that in these cases the dilated bronchial arteries might perform this function, and this is usually the case. The lungs were supplied from the left subclavian in Chambers' case, from a dilated ductus arising from the left subclavian in Ramsbotham's. In a case reported by Voss two large bronchial arteries passed into each lung, and were accompanied by an anomalous branch from each coronary. In Koller-Aeby's case the ductus was absent, and three large vessels, equalling the carotid in size, arose from the upper thoracic aorta at the site of origin of the bronchial arteries. The first turned to the right lung, following the bronchi; the others were given off as a common trunk, which divided into a larger branch going to the right and a smaller to the left lung.

Pathogenesis.—Two problems are presented. (1) Is the stenosis of inflammatory or of developmental origin? (2) What is the relation of the septal defect so often associated?

It must be recognized that a small group of cases occurs in which the stenosis is strictly limited to the valves and no septal defect is associated and which present appearances identical with those produced by the chronic valvular disease of postnatal life. Such cases must be supposed to be the result of an endocarditis in later fetal life.

In the large majority of cases a defect of the interventricular septum is associated, indicating that if the stenosis be due to an endocarditis, this must have occurred before the development of the heart was complete at the end of the second month of gestation. It is upon these cases that the discussion really turns. It is evident that if endocarditis can take place during the later stages of gestation, it may occur earlier as well. On the other hand, there are many cases in which the presence of associated defects and the absence of inflammatory action show positively that arrest of development has been the cause. The view is now generally held that in the past far too great weight has been laid upon the part which inflammatory processes take in the etiology of the many forms of pulmonary stenosis which date back to early embryonic life, before the development of the heart was completed. The theory of fetal endocarditis as a cause must now be considered to be of but limited application. The fault lies undoubtedly in most cases in a primary arrest of development.

Reference has been made to the explanation communicated by Keith, which is now generally accepted, that in the majority of cases the stenosis is primary in the conus, and is the result of an arrest of development at a stage when there existed in the heart a fourth primitive chamber, the bulbus cordis. In accordance with the researches of Greil, he de-

scribes three changes as taking place in the evolution of the mammalian from the primitive heart of the fish and reptilia: (1) The division of the primitive auricle and ventricle; (2) the submerging of the sinus venosus in the musculature of the right auricle; and (3) the separation of the bulbus cordis from the left ventricle and aorta, and its complete incorporation in the right ventricle as the infundibulum of that chamber. This last change takes place by an upgrowth of the ventricular musculature around the cavity of the bulbus, the musculature of the latter being replaced by that of the ventricle, in the same way as the musculature of the auricle replaces a great part of that of the sinus venosus. The author considers that "*the submergence of the bulbus constitutes a critical phase in the developmental metamorphosis of the heart, and it is during this time that malformations are apt to occur.*"

Four different types of conus stenosis are distinguished by him, of which the first is that well-differentiated form in which the conus forms a separate chamber, being separated from the sinus by a muscular partition. Peacock, in describing a similar case, compared it to the three-ventricled heart of the turtle, and considered that it represented an arrest of development. Keith explains the condition as being simply an arrest of development in which the infundibulum and body of the right ventricle have developed to a normal extent, while a constriction has remained between them, *representing the ventricular origin of the bulbus* or a persistence of the lower bulbar orifice. The other forms of conus stenosis, in which there is a constriction more or less complete of the whole infundibulum, he explains as an arrest of development of the bulbus as a whole, its musculature failing to become submerged in that of the right ventricle proper.

Associated Anomalies.—Grave cardiac defects are frequently associated, especially in pulmonary atresia, and constitute another argument in favor of a developmental origin. In Ettlinger's case there was a large defect in the interauricular septum above, with multiple defects of the interventricular septum, and the pulmonary veins opened into the right auricle. In Habershon's there was false dextrocardia, tricuspid stenosis, defect of the interventricular septum, and horseshoe kidney.

A fact of much importance is the presence of associated anomalies in cases of atresia with *closed* ventricular septum, which might reasonably be considered to be of inflammatory origin. It seems probable that the primary condition here was a narrowing of the conus or orifice in an arrest of development, and that the obliteration was produced by an endocarditis supervening in later fetal life.

Symptoms.—The majority of cases of pulmonary stenosis and atresia present the classical picture of congenital cyanosis in all its details. So frequent is the association between the two conditions, that *morbus cæruleus* and pulmonary stenosis have been considered almost synonymous terms. The clinical aspects vary to a certain extent with the presence or absence of defects of the interventricular septum, and with the degree of deformity. In stenosis with closed septum cyanosis is usually slighter and of later incidence, and the duration of life much longer. The most typical instances of congenital cyanosis with bluish discolora-

tion of the skin, becoming pronounced on exertion, clubbing of the fingers, dysnpœa, and cyanotic attacks are seen in the many cases in which pulmonary stenosis is combined with defect of the septum and *rechtslage* of the aorta. Pulmonary atresia differs from a simple stenosis in the more extreme degree of the cyanosis. These are the cases of true *morbus cæruleus*, in which a constant deep blue, or even purple, discoloration exists, increasing to black on violent exertion. Here the opposite condition in relation to septal defects is seen. When the septum is closed the cyanosis is more extreme and the duration of life correspondingly shorter. Pulmonary stenosis with defect of the septum in which no cyanosis is present is exceedingly rare, but a few cases are on record.

Physical Signs in Pulmonary Stenosis.—These are generally distinctive, but may be obscured by those of the septal defect so often associated. In typical cases, enlargement of cardiac dulness to the right and above, precordial bulging, epigastric and precordial pulsation indicate an enlargement of the right heart. Sometimes the cardiac impulse may be so violent that the head and neck share in the vibration of the chest. A thrill, localized to the second and third left spaces, or diffuse over the precordium, is fairly frequent. Its presence seems to depend somewhat upon the condition of the septa. Rolleston,[1] in reporting a case of stenosis with *rechtslage*, in which there was no precordial thrill, explains this by the presence of a large defect of the septum, through which the blood current passed with ease into the aorta. He says that the evidence in recorded cases is contradictory upon this point, and suggests a statistical study of it. A thrill was present in 17 of the 82 "primary" cases analyzed. In these the condition of the fetal passages was as follows:

Cardiac septa.	Number analyzed.	Number with thrill.
F. O. and V. S. closed	7	3
F. O. patent and V. S. closed	11	4
F. O. patent, defect V. S.	24	7
F. O. closed, defect V. S.	40	3

That is to say, in more than a third of the cases with closed ventricular septum a thrill was present, as also in 7 of the 24 in which both foramen ovale and ventricular septum were open. But in the 40 cases with closed foramen ovale and with defect of the septum a thrill was absent in all but 3; in one of which there was a large patent duct, which was apparently the cause.

These figures are puzzling at first, but interesting on reflection, and are large enough to be of value as facts. The inference is that a thrill is frequently present when the interventricular septum is entire, and also when a defect of that septum coexists with a widely patent foramen ovale; when the interauricular septum is closed and the interventricular open a thrill is rare, and when it does occur may perhaps be ascribed to the associated septal defect. Further statistics are needed.

The pulmonary second sound is weak or absent in a certain proportion of cases. Much stress has been laid upon the absence of pulmonary accentuation as a diagnostic sign of pulmonary stenosis, but in a number it has been distinctly louder than normal.

[1] *Trans. Path. Soc.*, London, 1892, xliii, 32.

A prolonged, harsh, rasping, or blowing systolic murmur heard over the whole cardia, but chiefly at the base, with its point of maximum intensity over the upper part of the sternum and the second left space, is present in the great majority of cases. It is transmitted upward toward the clavicle, along the course of the pulmonary artery, and over the sternum, but is faint or inaudible at the apex and to the right of the sternum. It may be so loud as to be heard over the whole chest. From this type important variations occur. (1) The murmur may be heard over the whole cardia, but with maximum intensity at the apex, as in Cassel's case, a boy aged thirteen years, with pulmonary stenosis and a patent foramen ovale, but the ventricular septum entire. In a case of Peacock's there was a loud systolic murmur over the whole heart and along the sternum, the maximum intensity of which was at the inner side of, and immediately above, the left nipple. In this instance a septal defect was associated. (2) In cases in which the septal defect is present the murmur may be heard over the *aortic* area and *along the carotids*. Eisenmenger mentions this as a diagnostic point for the association of pulmonary stenosis with a septal defect. In Scheele's[1] case, a girl aged fifteen years, with marked cyanosis, the pulmonary orifice admitted a thin pencil, the valves were small and shrunken, the conus was reduced to the size of a pea, and the septum was defective at the base. There was a systolic murmur along the course of the pulmonary artery and at the left sterno-clavicular articulation, which was transmitted far up the carotids and along both subclavians, and was most marked over the left carotid. It was heard also at the aortic cartilage. (3) The murmur may be heard in the back, in the left infrascapular region. This occurred in a number of the cases in this series, but in all a septal defect was associated, to which the transmitted murmur was probably due. (4) In a few cases physical signs are absent. Variot reports a child aged five years, with a large defect of the septum, and the pulmonary a small thin cord with rudimentary valves, who presented marked cyanosis with clubbing, but whose heart sounds were clear.

Diagnosis.—In the majority of cases the decided localization of murmur and thrill, the increased cardiac dulness to the right, the absence of pulmonary accentuation, and the presence of the distinctive symptoms of pronounced congenital cyanosis make a positive diagnosis possible. On the other hand, the variation in the character of the murmur and of the pulmonary second sound, and the occasional absence of cyanosis, render the diagnosis indefinite in a certain proportion of cases. That such atypical cases occur also makes it very difficult to exclude the possibility of pulmonary stenosis in the differential diagnosis of other cardiac defects. The presence of constant and marked cyanosis, the distinctive character of the murmur, and the fact that it is not usually heard in the back, are points in favor of stenosis. In patency of the duct, pulmonary accentuation is the rule, in pulmonary stenosis it is the exception.

Both the associated defect in the interventricular septum and the pulmonary stenosis have frequently been diagnosed. The presence of

[1] *Deut. med. Woch.*, 1888, xl, 294.

a thrill speaks rather for a closed septum, or for cases in which the foramen ovale also is patent. In a large number of cases the presence of the two distinctive murmurs can be easily traced, that due to the pulmonary obstruction heard best at the base and transmitted beneath the clavicle, that due to the defect localized at the fourth space, heard also in the back, both harsh, but of the two, the pulmonary usually of a more blowing character.

Course.—The duration of life in pulmonary stenosis with closed interventricular septum is relatively high. Peacock reports a patient dying at forty-five years, and the lowest age in this series was four years. The possibility exists in such cases that the stenosis had advanced, or even originated since birth. In stenosis with septal defect death occurs earlier, but adult life is also sometimes attained. The maximum age in this series was twenty years. In pulmonary atresia life is very short. The patients with closed septum all die within the first few months. When a defect of the interventricular septum exists these subjects may live some years. The highest age recorded was thirteen years, in one of Peacock's cases. The table gives the duration of life in the cases in the series in which this point is mentioned:

PULMONARY STENOSIS.

Age at death.	V. S. closed.	F. O. closed, defect V. S.	F. O. patent, defect V. S.
Before 1 year	0	4	3
1 to 7 years	2	17	8
7 to 14 years	4	6	5
14 to 20 years	5	8	5
20 to 28 years	6	3	1
28 to 45 years	1	0	0
Number of cases analyzed	18	38	22

PULMONARY ATRESIA.

Age at death.	V. S. closed.	F. O. closed, defect V. S.	F. O. patent, defect V. S.
In first week	1	0	0
1 to 4 weeks	1	0	2
1 to 3 months	1	1	1
3 to 6 months	3	1	2
6 to 9 months	0	0	1
9 to 12 months	0	0	4
1 to 5 years	0	3	0
5 to 10 years	0	1	0
10 to 13 years	0	1	1
Number of cases analyzed	6	7	11

Many patients who survive until early adult life die, not of the lesion, but of pulmonary tuberculosis. The frequency of this disease in pulmonary stenosis and its grave prognosis can be no longer disputed. The cause of the predisposition seems to be: (1) The reduced blood supply to the lungs produces an anemic condition which favors infection; (2) the marked cyanosis usually present depresses the general powers of resistance and tends to destructive tissue metabolism; (3) the subjects of pulmonary stenosis frequently live to an age when tuberculosis is

likely to invade the organism when the nutrition is low. This last point is illustrated in an interesting way in this series. Among the 18 patients with closed septum, in whom the duration of life was longer, pulmonary tuberculosis occurred 7 times. Among the remaining 64 patients with defect of the interventricular septum (in whom life was shorter) it occurred in only 9 cases, making an incidence of 16 cases in the 82.

Another not infrequent termination is by infection from an acute endocarditis developing at the seat of the defect. Robinson reports two instances in patients who both died at the age of twenty years, in both of whom the conus formed a separate chamber with narrow bulbar orifice. In the one case there were large vegetations on the conus wall, in the other these formed a fine fringe around its ventricular orifice, and coarse outgrowths about the associated defect in the interventricular septum. Acute endocarditis appears to be especially common in this form of conus deformity, and among the 19 cases in which the conus formed a separate chamber, recent vegetations fringing the conus orifice, on the wall, or on the tricuspid valve were present in 6. In Saundby's case there was a vegetative arteritis of the pulmonary artery, but none of the valves.

DILATATION OF THE PULMONARY ARTERY.

Dilatation of the pulmonary artery is very common in combination with certain cardiac anomalies but is rare as an isolated condition. A few cases are recorded in which it appears to be primary and to originate in an irregular division of the common arterial trunk. The main vessel is diffusely enlarged and its branches are tortuous and dilated, but the heart and lungs are otherwise normal. The artery is usually dilated in persistence of the fetal passages connecting the two sides of the heart, especially in patent ductus and defects of the lower part of the interauricular septum, or in widely patent foramen ovale. In the two latter conditions hypoplasia of the aorta is frequently associated and it is difficult to say which is the primary condition. The dilated artery may be atheromatous even in young subjects.

In defects of the interventricular septum at the base, the hypoplasia of the pulmonary artery so often present may give place to a marked dilatation. This was the case in 9 among the 34 primary defects of the septum in this series. The clinical manifestations of pulmonary dilatation are discussed by Abrahams[1] with the report of a case in which this was diagnosed as the primary condition.

CONGENITAL AORTIC STENOSIS OR ATRESIA.

Subaortic Stenosis.—This term has been applied to a curious annular thickening of the endocardium of the left ventricle, a few millimeters below the aortic valves, which involves the base of the aortic segment of the mitral valve, and encircles the ventricular wall at this point, and

[1] *Jour. Am. Med. Assn.*, 1913, lx, 1150.

leads in most of the cases, to a localized narrowing of the cavity. The cases recorded are not numerous (seven in all), but the condition, when present, usually leads to serious results, and is therefore important. The thickened ring of tissue is often the seat of a chronic inflammatory process, probably of later incidence, but there can be little doubt that it is itself of congenital origin. Microscopic examination of the ring in a case reported by Moore showed it to be non-inflammatory in character. Keith explains it as an arrest of development, analogous to the conus stenosis of the right ventricle, the bulbus failing to atrophy about the root of the aorta.

Endocarditis frequently develops both at the defect and at the aortic valves above it, and may lead to further contraction at these points. Shennan[1] and Smart[2] report two such cases under the term "double aortic stenosis," and a third is recently recorded by Thursfield and Scott.[3] In the last, the aortic orifice was narrowed by a fibrous ring, situated on the interventricular septum, just below the undefended space and extending over the anterior mitral segment, and the aortic valves were thickened and fused; there was a thin line of fibrosis in the otherwise healthy aorta just above the margin of the valves, and slight coarctation at the isthmus. In Shennan's patient, and in that of Fletcher and Beattie, a thick calcareous ring lay below the thickened and ulcerated valves which were the seat of a malignant endocarditis.

Most of these patients reach adult life, and the clinical significance of the condition lies chiefly in the frequent incidence of acute endocarditis. The picture is that of an acquired aortic stenosis. Slight symptoms may exist from childhood, or no sign of the presence of the defect may be given until an acute endocarditis develops, or failing compensation sets in. The systolic murmur produced by the constriction may be very rough, and audible some distance from the chest wall. A precordial thrill existed in some cases.

Congenital Stenosis and Atresia of the Aortic Orifice.—Aortic stenosis of antenatal origin is not common and the duration of life with it is very short. Two forms may be distinguished; those apparently inflammatory, with the stenosis limited to the valves and the ventricular septum entire, and those apparently due to an arrest in development. Unlike pulmonary stenosis, the inflammatory forms are here the commoner, fetal endocarditis, although rare in the left heart, usually involving the aortic orifice. Thérémin collected 17 cases, in only 2 of which was there a defect of the septum. In our series there are 6 cases, 5 of which are inflammatory.

Mönckeberg[4] reports a case of inflammatory origin in an infant of four days, and refers to 12 cases in the literature. He ascribes the occurrence of the fetal inflammation to probably the fifth month of gestation, for the left heart was very small, and the right side so hypertrophied that the apex of the right ventricle formed a recess-like cavity below the left, a condition typical of a heart in which the right ventricle had carried on the systemic circulation through the ductus arteriosus

[1] *Lancet*, 1905, vol. i, 21.
[2] *Ibid.*, 1904, vol. ii, 1417.
[3] *Brit. Jour. Child. Dis.*, 1913, x, 104.
[4] *Deut. path. Gesell.*, 1907, xi, 224.

for a long time. In aortic atresia the left ventricle is aplastic, and when a defect of the septum exists, may even be obliterated. The foramen ovale and ductus, are nearly always widely patent, the latter supplying the systemic circulation.

Cyanosis is usually slight or absent in cases of aortic stenosis, but marked in atresia. Physical signs may be absent, or there may be a loud systolic or double murmur heard over the whole chest. In both conditions the duration of life is very short. In aortic atresia the highest age attained was twenty-seven weeks. Simmons[1] described an interesting case in an infant aged sixteen weeks, cyanotic from birth, with widely patent foramen ovale and ductus arteriosus, the left ventricle aplasic, the right ventricle greatly hypertrophied, and the aortic cusps fused to form a cone.

Left-sided Conus Stenosis.—Schmincke[2] describes two cases in adults of a peculiar muscular stenosis of the conus of the left ventricle, with healthy aortic valves, and no apparent cause, which he thought must be of congenital origin, due to a primary asymmetry in the formation of the left ventricle.

ANOMALIES OF THE SEMILUNAR CUSPS.

These cusps may be increased or diminished in number and defective, fenestrated, or otherwise malformed. A row of supplementary cusps may exist or they may be the seat of attachment of anomalous bands.

Increase in Number.—Supernumerary cusps sometimes occur in the pulmonary artery and, less frequently in the aorta. A more or less perfectly formed fourth cusp of varying size, but frequently smaller than normal, may be inserted between two of the others. Or the usual number of segments may exist, and the sinus behind one of these be divided by a raphe which runs from the back of the cusp to the aorta, indicating fusion of the additional segment or imperfect division from its fellows. In rare instances five cusps occur. Peacock figures a case of five aortic cusps, and Dilg enumerates from the literature 4 cases, in 2 of which the five cusps were in the aorta, and in the pulmonary artery.

The supernumerary cusps have sometimes been explained as an effort at repair of some inflammatory process of long standing, but when the fourth segment is perfectly formed, or the raphe indicating it shows no sign of thickening (as in a case in the McGill Museum), a true malformation must be concluded, which is usually explained as a formation by excess. As this condition is of congenital origin, the cusps are generally so adapted to each other as to be competent to close the orifice, no insufficiency resulting; they occur usually in a heart free from other malformations, and are of very infrequent occurrence. Their clinical significance is slight, and lies chiefly in their tendency, like all valvular anomalies, to become the seat of endocarditis.

Diminution in Number.—A bicuspid pulmonary valve is not uncommon with other cardiac anomalies, especially transposition and septal defects. A bicuspid aortic valve usually occurs in an otherwise normal heart or

[1] *Intercol. Jour. of Austral.*, February 20, 1906.
[2] *Deutsch. med. Wchnschr.*, 1907, xxxiii, 2082.

associated with coarctation or hypoplasia of the aorta. In some instances both pulmonary and aortic valves may be bicuspid. The anomalous segments may be large, with smooth surfaces, showing no sign of further division, a true reduction in number existing; or one or both may present on the arterial aspect a ridge or raphe imperfectly dividing the sinus behind it into two parts, and indicating either a fusion of two formerly independent segments or a beginning separation of a single cusp into two elements; in other instances a single membranous ring or diaphragm may exist with two such raphes on its aortic surface, indicating the union with each other of all three cusps. Where such a raphe is absent, the condition is undoubtedly a true malformation, but where this exists, the origin of the bicuspid state of the valve admits of much discussion. Peacock arrived at the conclusion that the majority of cases were congenital, due either to an original malformation or to fusion in a fetal endocarditis.

A series of cases illustrating the same line of thought was published by Osler.[1] As pointing to a fusion originating in fetal life, he enumerates (1) the presence of a low, sometimes half obliterated, raphe behind one of the cusps; (2) compensatory changes in the fused cusps, so that their free edge becomes equal to or even shorter than the single segment; and (3) the fusion of the coronary or right and left segments of the valve. That the lateral (right and left) segments are the seat of the congenital fusion, the posterior cusp remaining always single, is stated also by Birch-Hirschfeld.

Thickening of cusp and raphe does not prove that the fusion is not of congenital origin, for endocarditis is likely to supervene on any valvular anomaly. On the other hand, it is admitted that many cases are of postnatal inflammatory origin. Such postnatal fusion may be reasonably deduced when (1) the two sections of the cusp are approximately equal; (2) when the raphe dividing them has its superior origin on a level with the superior origin of the unaffected cusp (instead of at the lower level, as described by Osler); and (3) *when in addition the only thickening observable is in the angle between the fused cusps.* This latter point has been called to the attention of the writer by Dr. Adami, who points out that the free part of the cusps, being in constant motion, is but little liable to undergo inflammatory adhesion, and that this will be prone to occur at the point of their insertion into the orifice wall, which is the only portion of their edge that is fixed and relatively motionless. Therefore, inflammation originating at the angle of junction of contiguous cusps may lead to localized obliteration of the primary angle, or to fusion of the cusps with a new immovable angle of junction further removed from the aortic wall, a progressive fusion occurring.

When a thin delicate raphe exists behind one of the segments of a bicuspid valve without any trace of thickening, Babes insists that it cannot be ascribed to a fusion in fetal endocarditis, but must be regarded as a true malformation dependent perhaps on incomplete division of an originally single cusp. The semilunar cusps originate from the four distal

[1] *Montreal General Hosp. Reports*, 1880.

bulbar endocardial ridges, two of which are divided by the descent of the aortic septum, so that a third segment is placed in each artery. The four cusps of the undivided truncus are sometimes seen in the cases of common arterial trunk.

The results upon the heart and circulation of a reduction in the number of the aortic cusps may be summed up as follows:

1. The segments may approximate and be perfectly competent, no pathological effects ensuing. This is proved by the occasional finding of a bicuspid valve in healthy adults even of advanced age.

2. The gradual bulging of the cusps, their greater length, the free space that sometimes exists between them, perhaps a yielding of the aortic ring, lead frequently to a valvular insufficiency or to a narrowing of the orifice.

3. Endocarditis commonly supervenes, either as the acute, often malignant form, or as a chronic inflammatory process, leading to thickening and deformity of the cusps and to subsequent valvular disease.

4. Atheromatous changes at the base of the aorta have been frequently noted, and in 6 of the 11 cases described by Babes and Deteindre there was an aneurismal bulging of the right posterior wall of the aorta, which formed in 5 instances a definite aneurism, from the rupture of which, in 2 cases, death ensued. This is seen also in two cases in the McGill Museum.

This remarkable combination of an aneurism of the base of the aorta with a bicuspid valve is believed by Babes to be directly connected with the bicuspid character of the aortic cusp below it, and is ascribed by him (*a*) to an extension of the same thinning or trophic process that led to the anomalous condition of the cusp, (*b*) to the lack of support given to the aorta at this its weakest point, and (*c*) to the frequent insufficiency of the cusps and the yielding of the aortic ring.

Miscellaneous Anomalies.—Dilg reports a remarkable case, in a child aged two years, of an endocardial fold divided roughly into two cusps with their convexity toward the ventricle, just below the base of a bicuspid aortic valve, both coronaries being behind one cusp. Banks[1] reported a woman, aged thirty-four years, with physical signs of aortic insufficiency and a loud, musical murmur at the base, audible at some distance from the chest, whose heart was hypertrophied and presented a cribriform condition of the aortic valve, and one-quarter inch below it in the left ventricle three other rudimentary cusps. These may be of compensatory, postnatal origin, as in a number of other cases recorded of long-standing aortic insufficiency.

In a case in the McGill Museum, reported by Campbell and Hepburn,[2] of pulmonary conus stenosis with septal defect, two well-formed valves are situated 1.8 cm. behind the pulmonary semilunar cusps, at the point which marks the lower bulbar orifice, and the site of the proximal bulbar swelling in the embryo. This is an entirely unique finding and suggests an atavistic reversion to the cusps seen at this point in the dipnoan heart.

In one of Babes' cases of bicuspid aortic valves, a peculiar band, like

[1] *Dublin Hosp. Gazette*, 1857, p. 330.
[2] *Can. Med. Assn. Jour.*, 1913, iii, 871.

a papillary muscle of the mitral valve, traversed the sinus of Valsalva. Hektoen[1] quotes from the literature several other instances of anomalous cords at the level of the valves, and a case observed by himself of a large defect at the base of one of the segments, all of which he ascribed to defects in the development of the aortic septum.

Defective Development of the Semilunar Cusps.—In a few instances of bicuspid valve a gap may be left on the wall of the vessel between the segments where evidently no third cusp has formed. This occurred in two of Deteindre's series. A remarkable instance of such a defect in the pulmonary valve is recorded by Stinzing. Here there are only two pulmonary cusps, and a large free space occupying the position of the third was traversed by two low ridges, evidently its rudiments. The heart was from a woman, aged sixty-four years, presenting signs and symptoms of pulmonary insufficiency, a history of pneumonia eight months before death, and failing compensation since.

PRIMARY DEFECTS OF THE AURICULOVENTRICULAR ORIFICES.

Congenital disease of the auriculoventricular valves differs from that of postnatal life chiefly in its infrequency, in the more extreme character of the process, atresia being more common than stenosis, and in the fact that the right side of the heart is usually affected rather than the left. Owing to the rarity of the cases, to the short duration of life, and to the fact that in the infant heart the picture presented is hard to distinguish from that of the more frequent lesions at the arterial ostia, this subject is not of great clinical importance, and its chief interest lies in the contribution which it brings to our information upon the question of the pathogenesis of cardiac defects.

Tricuspid Stenosis.—Although this lesion is not very uncommon in adults the cases which can be proved to have originated in intrauterine life are very rare. Vierordt knew of only three instances, unassociated with disease of the pulmonary valves, in the literature. In combination with pulmonary stenosis or atresia it is more frequent. A good illustration of the latter combination is seen in a specimen in the McGill Museum, presented by Sir William Osler. In the heart of a cyanotic infant aged four months, both pulmonary and tricuspid valves are thickened, shortened, and fused, and their orifices markedly reduced; the ventricular septum is entire, the foramen ovale widely patent, the right auricle hugely dilated, and the tricuspid surmounted by recent vegetations. Such cases are undoubtedly of inflammatory origin, and are of value as proving that fetal endocarditis, although it has been overrated as a cause, certainly has its place as an etiological factor in congenital cardiac disease.

Tricuspid Atresia.—Although in itself rare, tricuspid atresia is the commonest of all congenital lesions of the auriculoventricular cusps. Rauchfuss collected 16 cases from the literature of which 5 were due to a defect in development, 5 were apparently inflammatory, and the remainder were of "doubtful" origin. Since then additional cases have

[1] *Chicago Path. Soc.*, 1905.

been reported by Chapotot (quoted by Vierordt), Sieveking, Kühne[1] (two cases) Bernstein[2] and Wieland.[3]

Pathological Anatomy and Pathogenesis.—Cases of inflammatory origin must be distinguished from those due to a defect in development, for the latter present several points of special interest. Those of inflammatory origin have usually progressed through a stenosis and show distinct evidence of an antenatal valvulitis in the form of an extensive cicatricial contraction of the endocardium adjacent to the obliterated tricuspid orifice, and often of the pulmonary valves. The developmental cases, on the other hand, may present no sign of inflammation, but the tricuspid orifice is absent, and either shows no trace of its presence, or this is marked by a shallow groove, the tricuspid segments are lacking, and the right auricle is divided from the right ventricle by a thick muscular septum. Kühne, and subsequently Wieland, subdivided these developmental cases into a group of (*a*) "isolated" primary atresias in which certain pathological changes of a secondary nature are constant so that a definite type is set up, and (*b*) tricuspid atresia complicated by other grave cardiac anomalies of independent origin, such as transposition of the arterial trunks, pulmonary atresia, etc. Eight cases of the "isolated" form that constitutes the first group were separated by Kühne, and later by Wieland, from the others. To these may be added one by Bernstein from our series. The changes in all of these are practically identical and clearly indicate the sequence of events. There is an entire absence of the tricuspid orifice, and the body of the right ventricle is an aplastic structure, while the left is highly hypertrophied and dilated, appearing at first sight to form the whole heart, with the right chamber as an appendage to it; the right auricle is also hugely dilated and the foramen ovale is widely patent, or a defect of the interventricular septum exists; in addition there is always a defect in the muscular interventricular septum leading from the cavity of the left ventricle into the dilated conus of the right ventricle and thence into the pulmonary artery. The course of the circulation is necessarily from right to left auricle through the foramen ovale, and thence to the left ventricle, from which the blood is distributed in part to the aorta and in part through the septal defect to the pulmonary artery. The aorta is usually dilated, and the pulmonary is normal or somewhat reduced in size owing to the smallness of the chamber from which it springs.

These cases of "isolated primary tricuspid atresia" are of interest from the standpoint of the pathogenesis of ventricular septal defects, for they show that the old mechanical or congestive theory of septal defects in pulmonary stenosis, in which the defect was thought to be secondary to the raised pressure in the right ventricle, which has long been justly discarded in this connection, at least in regard to the developmental forms of pulmonary stenosis, must be accredited here. That is to say, the septal defect in tricuspid atresia is here evidently secondary to the congestion in the left ventricle which forces an outlet in the conus

[1] *Jahrb. f. Kinderh.*, 1906, lxiii, 235.
[2] *New York Path. Soc. Reports*, February, 1906.
[3] *Jahrb. f. Kinderh.*, 1914, lxxix, 320.

of the pulmonary artery and this allows the circulation to be maintained. Wieland points out and insists on the importance of Kühne's separation of this group, with its constant secondary complex, on this account.

It should be remembered that cases of developmental tricuspid atresia with or without complicating cardiac anomalie, constitute one well recognized form of the cor biatriatrum triloculare. The subject is discussed under that head.

Etiology.—The causation of the cases of inflammatory origin is that of fetal endocarditis elsewhere. In tricuspid atresia the secondary ventricular septal defect is bound to occur, for the proper maintenance of the circulation as well here as in the developmental forms.

Much interest attaches to the causation of the developmental forms of tricuspid atresia. In the embryo the auricular canal opens at first by a common orifice into the left side of the common ventricle, and later by a process of shifting to the right comes to lie more in the median line. The theory had been advanced that either a lack or an exaggeration of this shifting to the right would lead to a wrong adjustment of the parts, and to a mitral or tricuspid atresia. Again, the auriculoventricular orifice is divided into the mitral and tricuspid ostia by the growth of endocardial cushions in its centre, and by a union of these with the interauricular and interventricular septa. Should these cushions become deviated to the right or to the left in their formation they may become adherent to the corresponding wall of the common ostium and thus lead to tricuspid or mitral atresia. Rokitansky thus explains his case of mitral atresia. In that by Robertson the tricuspid atresia present was ascribed to a fusion of the endocardial cushions with the malposed auricular secondary septum, in consequence of a persistence of the valvulae venosæ which formed a coarse network across the cavity of the right auricle. The suggestion has also been made that a premature obliteration of the ductus arteriosus during early fetal life, might lead to aplasia of the right ventricle and tricuspid orifice by cutting this part of the heart out of the fetal circulation. This possibility is disproved, however, by the fact that in several of the cases this passage is freely patent. The conclusion remains that the probable causation of mitral and tricuspid atresia lies in the mal-position and irregular union of those parts of the cardiac septa dividing the mitral from the tricuspid ostium.

Symptoms and Signs of Tricuspid Stenosis not Atresia.—Cyanosis may be present from birth, or may develop after a few days or weeks. In the classical developmental type described above it is usually extreme in the end, though its onset may be delayed for some time. In Bernstein's case, aged two years and eight months, it did not appear until the sixteenth month, but then became marked with clubbing, and a polycythemia of 10,000,000 developed. This late appearance was possibly explained by the absence in this case of the auricular septum, a condition which must have facilitated the circulation. On the other hand, Kelley's patient, a delicate, unhealthy child, showed only slight lividity on crying or when he had a cold, and in Sieveking's case, dying at nine weeks, cyanosis was absent throughout, but dyspnœa was a prominent symptom.

Dyspnœic attacks are a prominent feature, are often of daily occurrence and are frequently the direct cause of death.

Physical signs are not very characteristic, being obscured by those of the septal defect that in tricuspid atresia is always present, and by the fact that a systolic murmur with maximum intensity over the right ventricle, such as is usually produced in these cases, may with difficulty, be distinguished from one generated at the pulmonary area. The marked hypertrophy of the left combined with the smallness of the right ventricle is of assistance in the differential diagnosis from pulmonary valve disease, although allowance must be made for the increased cardiac area produced by dilatation of the right auricle. This feature was indicated in Wieland's patient by a zone of dulness to the right of the vertebral column behind. His case was characterized also by a strong systolic murmur and precordial thrill of maximum intensity at the apex, both of which were of a *curiously intermittent character.*

Duration of Life.—Very few of the developmental cases of tricuspid atresia live more than one year. Bernstein's patient reached two years and eight months, a relatively high age that is perhaps explained by the almost complete absence of the interauricular septum that was present. In the inflammatory cases, in which the atresia has probably progressed through a stenosis, adult life is frequently attained. Such was Bierdach's case dying at twenty-eight years.

Congenital Mitral Stenosis.—This is even rarer than the same lesion at the tricuspid orifice. A typical case evidently due to an antenatal valvulitis, in a child of ten months, with cyanosis and dyspnœa from birth, is reported by Simmons. A curious combination of dwarfism and mitral stenosis in patients who have attained adult life has been observed. L'Abbe reports a case in a woman, aged twenty-seven years, of extremely small stature (1 meter high, 43 kilos weight), puerile intelligence, and marked infantilism. There was a clear history as well as physical evidence of congenital syphilis, and a pure mitral stenosis.

Mitral Atresia.—A complete obliteration of the mitral orifice is still rarer than stenosis. The same remarks apply in regard to etiology as in tricuspid atresia, but here a primary defect in development may be almost constantly assumed. Grave associated anomalies are also nearly always present, and give additional proof of a teratological origin. In Thérémin's observation of an infant aged two days, the left auricle and ventricle were aplastic without any trace in the latter of a mitral orifice, its walls being formed throughout of finely reticulated muscle fibres; the foramen ovale was closed, the interventricular septum defective, the pulmonary valve bicuspid, and the aorta appeared to arise from the right ventricle; there was a *horseshoe kidney and double ureter.* Lawrence and Nabarro give a similar case of mitral atresia, defect of the septum, aplastic left ventricle, the aorta arising behind the pulmonary artery from the right ventricle, with *coarctation of the aorta, transposition of the stomach, absence of spleen and hepatic section of inferior vena cava; anomalies in form of liver and lungs.* In Rokitansky's case of aortic and mitral atresia with defect of the septum, patent foramen ovale,

and dilated pulmonary artery, in a child aged twelve days, there was an *accessory right bronchus*.

Congenital Mitral and Tricuspid Insufficiency.—These lesions may result from a primary malformation of the cusps or from secondary deformity in the arrest of development of neighboring structures, as in persistent ostium primum. Or they may be due to thickening and shortening of the valve in a fetal endocarditis; thus Barth and Roger describe a case in which, on auscultation before birth, a long, loud, rough murmur was heard accompanying the heart sounds. The child was stillborn three days later, and the right ventricle was found dilated, the tricuspid orifice enlarged, and its cusps shrunken and insufficient, and evidently the seat of an endocarditis. In the case of Steffen, of a child aged ten and a half months, there were no tricuspid segments, but the valve formed a low ridge which was thickened, reddened, and slightly jagged. The mitral cusps were similarly thickened and reddened, and one of them was reduced likewise to a narrow ridge.

Congenital Mitral Insufficiency.—Steffen's case is the only instance of congenital mitral insufficiency found in the literature. True congenital tricuspid insufficiency is also rare, probably there are not a dozen cases.

ANOMALIES OF THE AURICULOVENTRICULAR CUSPS.

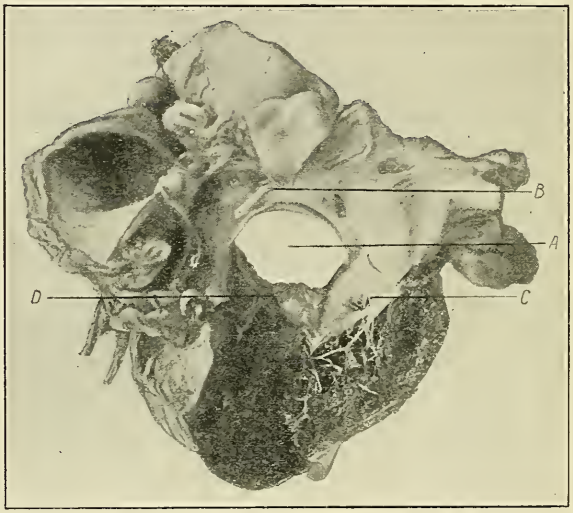
Double Auriculoventricular Orifice.—A second valvular opening supplied with its own cusps, chordæ tendineæ and papillary muscles, may lie within the segments of an otherwise normal auriculoventricular valve. Seven such cases are recorded, six of double mitral orifice by Greenfield,[1] Cohn,[2] Degen,[3] Stuhlenweisenberg,[4] and Camisa,[5] and one of double tricuspid by Pisenti.[6] In Stuhlenweisenberg's case, and in one of Camisa's, the two orifices were of equal size, and were separated by a bridge of valve tissue which supplied a cusp to either opening; in all the other cases the second opening was much smaller, and lay in one of the segments of the primary orifice.

Two hitherto unpublished cases of the latter description, are in the collections of the Harvard and the McGill Medical Museums. In the Harvard case, an opening 2 cm. long lies in the aortic cusp of the main mitral orifice, and leads into an aneurismal pouch formed by the apex of this segment, which communicates with the cavity of the ventricle by numerous fenestrations. The McGill heart (Fig. 37) is of bizarre external form owing to its bifid apex, deep auriculoventricular groove, and hypertrophied right chambers. The interauricular septum presents a small valvular patent foramen ovale above, and is absent in its lower two-thirds, a large crescentic defect (*persistent ostium primum*) existing. The mitral valve is replaced by a single large segment which is cleft in its anterior portion, passing forward from either side to be inserted

[1] *Trans. Path. Soc.*, 1876, xxvii, 128 (with plate).
[2] *Inaug. Dissertation*, Königsberg, 1896 (with plate).
[3] *Inaug. Dissertation*, Greifswald, 1903.
[4] *Centralb. f. Pathol.*, 1912, xxiii, 1027.
[5] *Ibid.*, p. 342
[6] *Di una rarissima Anomalia della tricuspide*, Perugia, 1888.

into the middle of the base of the interventricular septum where this bounds the interauricular defect below. The secondary mitral ostium lies in the posterior half of this large primary segment, 7 mm. back from its free margin. It is a perfect valvular opening admitting a lead-pencil with two well-formed cusps attached to slender chordæ, arising from two short papillary muscles which lie behind and independent of the single group from which the chordæ of the primary segment spring. The right auriculoventricular valve is malformed and an irregular excavation in its septal cusp suggests an unsuccessful attempt at a double tricuspid ostium. The aortic valve is bicuspid. The endocardium is healthy.

Fig. 37



Heart of a child, aged five years, showing; *A*, defect of lower part of interauricular septum; *B*, patent foramen ovale; *C*, double mitral orifice; *D*, cleavage of mitral segment. (From a specimen in the Pathological Museum, McGill University.)

Etiology.—Camisa believed a fetal endocarditis had led to a fusion of segments at their apices and to the formation of secondary orifices. Cohn and Stuhlenweisenberg suggest a malformation by excess, a view supported in the latter's case by the equal size of the two orifices. Pisenti supposed a fenestration of the endocardial cushions, which had transmitted the blood stream in early embryonic life and had become transformed into a second valvular orifice by a natural adaptation of growth, the papillary muscles and chordæ growing up to its borders.

In the two specimens seen by us, Pisenti's explanation seems to apply, the marked irregularities in both auriculoventricular valves due to the auricular septal defect in the McGill specimen, and the multiple fenestrations in the Harvard case, alike arguing for such accidental origin at an early embryonic period. Camisa's theory of a fetal endocarditis is not tenable in the case of the McGill specimen and others in which the endocardium is free from every trace of sclerotic change.

Symptoms.—The double orifice is in itself of no clinical significance, the secondary segments functioning as normal valves. In the majority of the cases, including Cohn's patient, who died at seventy-one years, both sets of valves were thin, healthy and competent. Chronic endocarditis had supervened in both Camisa's cases and in Stuhlenweisenberg's. In the latter a loud systolic murmur over the precordium was associated with insufficiency and sclerosis of the segments of the *anterior* mitral ostium, the posterior remaining free.

Displaced Orifice.—A double mitral orifice is described by Andrewes,[1] in which two orifices separated by a fibrous septum lay one behind the other in the left ventricle. The right ventricle was rudimentary, the interventricular septum defective and the tricuspid valve absent. A deflection of the septum to the right so that both orifices are placed in the same ventricle was assumed.

Miscellaneous Anomalies.—Various minor defects, as irregularly formed or accessory leaflets and anomalous arrangement of the chordæ tendineæ or papillary muscles occasionally occur, and may in some instances contribute to an insufficiency of the valves.

PRIMARY PATENCY AND ANOMALIES OF THE DUCTUS ARTERIOSUS BOTALLI.

The ductus arteriosus of the fetus is a short, thick trunk, 10 to 15 mm. long, running from the left branch of the pulmonary artery directly after the bifurcation to the under side of the arch of the aorta just beyond the origin of the left subclavian artery, which serves to carry the unaërated blood, returned from the head and upper extremities, to the descending aorta, whence it passes to the placenta. At birth the ductus undergoes a rapid involution, its lumen becomes practically impermeable about the third week of life, the alterations in its wall, which lead to its permanent obliteration, going on for some months, and finally transforming it into the ligamentum arteriosum of later life. The average diameter of the patent ductus at birth is given by Vierordt at 5 to 6.8 mm. and by Thérémin as 4.8 mm. But when filled with fluid during life, or experimentally injected directly after death, it is found to be much larger. Thus in a series of infant hearts prepared by Klotz, in which he injected the ductus from the aorta with gelatin at autopsy, it was found in the newly born to be fully equal in size to the main pulmonary trunk. He ascribes its apparent smallness as usually seen postmortem to the firm contraction of the muscular wall.

The ductus may (1) remain patent throughout life, (2) undergo aneurismal dilatation, (3) it may be absent, or (4) it may have an anomalous origin or course.

Patency of the ductus is not infrequent in combination with other cardiac defects, especially those in which there is some serious interference with the pulmonary circulation. It occurred in 166 of this series of cases, in 21 of which it was combined with pulmonary atresia,

[1] *Trans. Path. Soc.*, London, 1903, liv.

in 14 with pulmonary stenosis, and in 23 with transposition of the great trunks. As an isolated condition it is among the more infrequent of cardiac anomalies. The first carefully recorded case of primary patency with autopsy findings, was diagnosed before death and published by Bernutz[1] in 1849. Six cases were collected by Almagro[2] in 1862, 12 by Gerhardt[3] in 1867, 20 by Wrany[4] in 1871, and 26 by Vierordt in 1898. Herxheimer enumerated all the above in 38 cases collected in 1910, while Wells,[5] in 1908, found 41. A careful analysis of 34 cases with, and 37 without, autopsy report was published by Goodman[6] in 1910, and there are important clinical studies by Hochsinger, Gillett,[7] Taylor,[8] and Wessler.[9] From these and other sources, 64 cases of uncomplicated primary patency with clinical history and autopsy reports, have been analyzed in this series. Of these, 18 are in infants under two years, and 46 in "adults" over this age. As of special interest, or not included by other writers, may be mentioned the cases by Hewitt,[10] Hall,[11] Kingsley[12] Thompson[13] and Carpenter[14] in infants; and Kaulich,[15] Fagge,[16] Darier,[17] Schrötter,[18] Drasche,[19] Garipuy,[20] Crouzet,[21] Greenhow,[22] Gibson,[23] Wells, Schnitzler, and Mead,[24] in adults, as well as 13 adult cases quoted below, in which the patency was complicated by acute infective pulmonary endarteritis.

Pathogenesis.—The causes of persistent patency of the duct are to be sought in the conditions of its normal closure, and this must depend upon the influences, mechanical or otherwise, of the changes in the circulation at birth, and upon the consequent alterations in the vessel wall, itself a fetal structure destined to involution. As *possible factors* in the process of closure may be enumerated: (1) peculiarities in the histological structure of the ductus wall, (2) alterations in the blood-pressure at birth, (3) modifications at birth in the position of the ductus relative to the aorta and pulmonary artery, and other mechanical factors preventing entrance of blood from the aortic side.

1. *Histology.*—The ductus wall is poor in elastic tissue as compared with the aorta and pulmonary artery, but is relatively rich in muscular elements, which, as well as the elastic tissue are known to undergo marked increase during the later months of intra-uterine life. More

[1] *Arch. Gén. de Méd.*, 1849, xx, 415.
[2] *Thèse de Paris*, 1862, p. 67.
[3] *Jena. Zeitsch. f. Med. u. Naturwis.*, 1867, Bd. iii.
[4] *Oestr. Jahrb. f. Pädiatr.*, 1871, Bd. i, p. 1.
[5] *Am. Jour. Med. Sc.*, 1908, pp. 136, 381.
[6] *Univ. of Penn. Med. Bull.*, 1910, xxiii, 509.
[7] *Gaz. d. hôp.*, 1910, 83, p. 1419.
[8] *Guy's Hosp. Gaz.*, May, 1901, p. 197.
[9] *Am. Jour. Med. Sc.*, 1913, cxlv, 543.
[10] *Trans. Path. Soc. London*, ix, 48.
[11] *Arch. Middlesex Hosp. Clin.*, Series XIII, 1913, p. 39.
[12] *Johns Hopkins Hosp. Bull.*, 1911, xxii, 239.
[13] *Edin. Hosp. Reports*, 1900, vi, 57.
[14] *Proc. Roy. Soc. Dis. Ch.*, 1909, ii, part 1, p. 163.
[15] *Viert. f. prak. Heilk.*, 1862, ii, 92.
[16] *Guy's Hosp. Reports*, 1873, xviii, 22.
[17] *Bull. de la Soc. Anat. de Paris*, 1885, x, 55.
[18] *Zeit. f. klin. Med.*, 1901, xliii, 161.
[19] *Wien. klin. Woch.*, 1898, xi, p. 1195.
[20] *Bull. de la Soc. Anat.*, February, 1907, p. 179.
[21] *Ibid.*, 1869, xiv, 323.
[22] *Clin. Soc. Trans.*, 1876, ix, 152.
[23] *Edin. Med. Journ.*, 1900, n. s., viii, 1, 212, 436.
[24] *Jour. Am. Med. Assn.*, December 24, 1910.

particularly a loose, subintimal layer of muscle is present (Thoma[1]); this evidently corresponds to Jore's musculo-elastic layer of the arterial wall, which is here developed both at an earlier period and to a greater extent than in the aorta and pulmonary artery. It is especially marked at either extremity of the duct where it can be seen to pass into and, indeed, to form, the musculo-elastic layer of the aorta (Klotz). When the canal is emptied of contents, as happens after birth, this increased muscularity enables it to contract firmly, so that its walls remain in juxtaposition and may undergo obliterative endarteritis.

2. *Alterations in the Blood pressure at Birth.*—Previous to birth, the pressure is highest in the right side of the heart; the pulmonary arteries are small, and almost all the blood passes through the ductus into the aorta. At birth the lungs are expanded, their capillaries are opened, and there is an immediate lowering of pulmonary blood pressure. Dr. Adami suggests that during the first few days of life the aortic tension, and therefore the mean blood pressure in the body as a whole, is also lowered, owing to the reduced amount of work which the heart is called upon to perform, after the cutting off of the placental circulation, and that this reduction in the mean blood pressure is the cause of the collapse of the ductus, and the main factor in closure. Kirstein also believes that a pressure equilibrium is established between the aortic and pulmonary circulations, which prevents a current through the ductus and thus permits of its obliteration, while Klotz thinks that alterations in the pulmonary pressure at birth, and the relative muscularity of the ductus wall are together sufficient to account for closure.

3. Nevertheless, *mechanical conditions preventing the flow of blood through the ductus from the side of the aorta* have been adduced by many workers, and may reasonably be supposed to assist in the process of closure, especially when the pressure in the aorta comes to exceed that in the pulmonary circulation. Schantz supposed a stretching of the duct by the movement of the pericardium, pulmonary artery, displaced thoracic organs, and sternum, in the initial respiration, and Strassman described, on the basis of a large number of injection experiments, a fold in the aortic wall at the upper border of the mouth of the duct, which appears about the seventh month, and which he thinks closes its opening in a valvular manner when the pressure rises in the aorta at birth. This theory of a valvular aortic fold has been widely accepted and has received recent confirmation in the experimental work of Fromberg.[2] Nevertheless, its constancy in infants, and its valvular action when present, has been gravely disputed by such careful observers as Klotz, Kirstein and Stiènon.[3] The last word on this subject has come from Stiènon, who has found that Strassman's fold is not shown on plaster casts of the ductus and adjacent vessels in the newly born, made under low pressure, and ascribes its appearance postmortem to the falling together of the canal after its evacuation. From the study of a large number of such casts of the aortic isthmus and of patent ductus at

[1] *Virchows Archiv*, 1883, vol. xciii, 443.
[2] *Baumgar. Arbeit. aus. d. Geb. d. Path.*, 1914, ix, 198.
[3] *Archiv. de Biol.*, 1912, xxvii, 801.

various ages, he concludes that the essential mechanical factor in closure is the *dilatation of the fetal isthmus*, which is produced by raised aortic tension after birth, so that the latter has the secondary effect of favoring closure by pressure of the dilated isthmus on the aortic end of the duct. Dislocation of the thoracic organs in the establishment of respiration probably also assists in diverting the circulation.

From the above considerations the general conclusion may be drawn that continued patency will occur (1) in conditions in which the blood pressure, either in the aorta or pulmonary artery, is maintained at a level approximating that before birth (as in atelectasis of the lungs), or in which, for any other cause, a high positive pressure in the ductus is maintained; (2) when a congenital defect in the structure of the ductus wall exists. That such a defect is not uncommonly the cause of patency is suggested by the frequent association of anomalies elsewhere in the body and by the not uncommon occurrence of a history of syphilis, or of anomalies in other members of the same generation, as in De la Camp's remarkable series of six brothers and sisters all with characteristic physical signs of patent duct.

That raised pulmonary pressure is usually at fault is evidenced by the frequent history of atelectasis of the lungs, difficulty in suckling or prolonged delivery in the mother, seen in the present series. In support of Stiènon's view, that dilatation of the fetal isthmus is an important factor, we may note that persistent patency is associated in most adult cases with a certain degree of coarctation of the aorta, and that the process of closure after birth is, like dilatation of the isthmus, a gradual one, extending over the first weeks of life and often not completed until the third month.

Pathology.—Three principal types of patency may be distinguished: (1) The duct may be greatly shortened upon itself so that its ends are approximated to each other, and it disappears as a canal, remaining as a simple aperture between the two great trunks. (2) More frequently the ductus persists as a short canal from 0.4 to 2 cm. long (Vierordt), with a lumen varying in size from one just admitting a bristle to one allowing the passage of a "goose-quill," "pencil," or even, as in Luys' case, the "finger." A patent ductus of long standing is usually shorter and broader than that of infancy or later fetal life. In form this canal may be (*a*) cylindrical, as is usual in infants, and as was seen in the cases by Fagge, Almagro, Gerhardt, and White[1] in adults; or (*b*) funnel-shaped (*i. e.*, conical, as in a funnel without a stem), with its larger end toward the aorta, as in a case by Murray, in which in a woman aged thirty-six years, it formed a truncated cone three-eighths of an inch long, just admitting a quill, and lying with its base to the aorta. Finally (following Gerhardt's classification into four types, of which the above forms 1, 2*a* and *b* constitute the first three), the patent duct may exist (3) as a canal which has undergone aneurismal dilatation.

In a patent ductus with otherwise normal conditions, the blood stream will be directed chiefly from the aorta, where the blood pressure is

[1] *Trans. Path. Soc.*, London, 1885, xxxvi, 182.

PLATE VI

Microscopic appearances of wall of patent ductus and adjacent aorta and pulmonary artery in a case of patent ductus arteriosus with acute infective pulmonary endarteritis, showing site of initial lesion at pulmonary end of ductus. Drs. Hamilton and Abbott. (Colored drawing by Dr. J. H. Atkinson.) (Haem. and eos. and elastic tissue stains. Low magnification.) A rectangular block has been cut to include the whole wall of the ductus (*D*, *D'*) and a portion of the pulmonary artery (*P.A.*) and aorta (*A*) adjacent. *A*, wall of aorta which is quite healthy. *P.A.*, wall of pulmonary artery. *D*, *D'*, wall of ductus arteriosus in which the elastic tissue is almost destroyed, and which is surmounted by a thrombotic mass (*B*). *C*, pulmonary end of ductus, showing destruction of elastica, and organization of inflammatory products (*i. e.*, seat of initial lesion). *E*, aortic end of ductus showing zone of recent inflammatory exudate and invasion of tissue between aorta and pulmonary artery by acute inflammation. *F*, necrosed area below ductus wall. *G*, recent acute inflammatory process extending from aortic end of ductus into cellular tissue between aorta and pulmonary artery. *H*, thrombotic mass overlying wall of pulmonary artery and becoming incorporated with it in neighborhood of pulmonary end of ductus.

higher, into the pulmonary artery. This is evidenced by the funnel-shaped form with its base toward the aorta, which the canal usually assumes in adults, and by the presence of mycotic vegetations on the adjacent wall of the pulmonary artery in all the cases of acute infective endarteritis in the neighborhood of a patent duct. Wagener's 3 cases, in which the membrane at the pulmonary end bulged into the artery, also indicate this direction of the stream. Dilatation of the pulmonary artery, and hypertrophy and dilatation of the right ventricle, are usual results of patency of long standing. Rauchfuss thought them characteristic of all cases, but exceptions occur. The left ventricle may share in the hypertrophy and the aorta be moderately dilated. In Fagge's case, a woman aged forty-two years, the right ventricle was greatly hypertrophied, being equal to the left in thickness; the right auricle was dilated, and the main pulmonary branches, especially the right, were much dilated. The left ventricle is occasionally hypertrophied in excess of the right. In rare instances, as in Walsham's and Drasche's cases, aged respectively forty-seven and twenty-nine years, the heart may not be hypertrophied at all.

Arteriosclerotic patches are not uncommon in the neighborhood of the patent duct in the aorta, and extensive atheroma may occur also in the pulmonary artery. In Hebb's[1] case the atheroma and dilatation of this trunk seem to be explained rather by the obliteration of its left branch through the pressure of the thrombosed duct.

Durno and Brown,[2] report a case in a man of thirty-three, of widely patent ductus arteriosus, with extensive atheroma both of the walls of the ductus, and of the greatly dilated pulmonary artery. A small saccular aneurism of the pulmonary close to the ductus had ruptured, forming a dissecting aneurism which in turn burst into the pericardium.

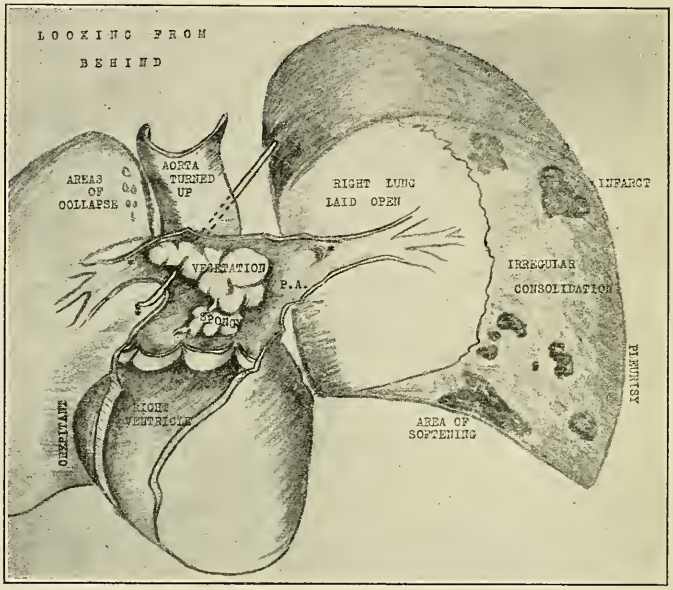
Acute Infective Pulmonary Endarteritis.—Vegetations of a malignant character are not uncommon within a patent duct, about its aortic orifice, and on the adjacent wall of the pulmonary artery. There are 13 such cases in our series; in all, the pulmonary artery adjacent to the ductus was extensively diseased, and in all but one (Hamilton and Abbott[3]), the heart valves were also involved in a malignant endocarditis. This last case was of especial interest because of the strict localization of the infective process to the ductus and the pulmonary artery adjacent, which showed clearly that the acute inflammatory process had originated in the immediate neighborhood of the defect, a point confirmed by microscopic examination, in which the organization of the inflammatory products proceeding at the pulmonary end of the ductus was clearly seen (see Plate VI), thus demonstrating this to have been in all probability, the earliest initial seat of a process, which had elsewhere and later assumed a fulminating, highly destructive character.

The patient was a girl of nineteen years, who presented a clinical picture of septicemia for some weeks before death, and the characteristic physical signs of patent ductus, without valvular involvement, or cyanosis. Postmortem a huge thrombotic mass of vegetations lay in the lumen of

[1] *Trans. Path. Soc.*, London, vol. xliv, 45. [2] *Lancet*, 1908, i, 1692.
[3] *Trans. Assoc. Am. Phys.*, 1914, vol. xxix (gives full bibliography).

the dilated pulmonary artery blocking the orifice of a large patent ductus, and extending into the left pulmonary artery (see Fig. 38). The aorta was stenosed at the isthmus but was otherwise healthy and the endocardium of the heart was free from every trace of disease. Embolic abscesses in the lungs, the vegetations in the pulmonary artery, and the blood culture during life contained swarms of pneumococci. Both the patent ductus and pulmonary endarteritis were diagnosed during life.

Fig. 38



Diagrammatic drawing showing acute vegetative endarteritis of pulmonary artery in the neighborhood of the patent ductus arteriosus, and consequent infarcts of the lung. A probe is seen passed through the patent ductus. (W. F. Hamilton and M. E. Abbott.)

The wall of the aorta opposite the ductus was the seat of the mycotic vegetations in some cases, indicating that the infection had proceeded with the current through the ductus and had impinged here.

Paradoxical Embolism.—In Schmorl's[1] case, an embolus passed from a primary thrombus in the left auricle, through a patent ductus arteriosus to the pulmonary artery. In the cases of acute infective pulmonary endarteritis enumerated above, septic infarcts in both systemic and pulmonary circulations, evidently from emboli passing through the patent ductus, were extremely common, occurring even in those cases in which only the tricuspid valve and pulmonary artery were diseased. Hochhaus based a correct diagnosis upon this feature.

Symptoms and Signs.—Clinical evidence of patency of the ductus is to be sought rather in physical signs than in symptoms, for the latter are often obscure. Nevertheless, their very negative character when

[1] *Verhandl. d. deutsch. path. Gesellsch.*, 1909, xiii, 217.

taken in combination with the distinctly characteristic physical signs, presents, in the majority of cases, adequate grounds for a correct diagnosis, and this can almost always be made. Careful contributions are now numerous, and a symptom complex has been built up which makes this chapter in congenital defects almost as legible to the clinician as that of any form of acquired cardiac disease. On account of the secondary anatomical changes that are usually induced in a patent ductus of long standing, such as shortening and widening of the duct and dilatation of the pulmonary artery, the picture in infants and early childhood, is somewhat different, and much less distinctive than that in later life. This statement applies especially to the physical signs.

The typical appearance is one of anemia, sometimes profound, which has been described as wax-like. Cyanosis is usually absent; when present it is generally slight and transient, appearing only on exertion, and usually develops late, sometimes as a terminal event. Of the 57 cases in which this point is mentioned, cyanosis was entirely absent in 27, of which 19 were in adults and 8 were in children under two years. Cyanosis was noted as slight in 13 cases, in one of which, Bittorf's (aged eleven years), it was constant, in the others transient, appearing only on crying in Simmons' (aged sixteen weeks), and during anginal attacks in Hale White's case (aged fifty-three years). It was moderate in 4 cases only. In that by Carmichael, dying at three, it came on soon after birth, becoming extreme, with clubbing and a polycythemia of 8,100,000. Coarctation of the aorta was associated with the patent duct, and mitral stenosis with great dilatation of the left auricle was present as well, suggesting a rise of pressure in the pulmonary artery and a possible reversal of flow, venous blood from this vessel entering the aorta through the canal.

Dyspnœic attacks usually accompanied by transient, but marked cyanosis, are relatively common in infants and are so characteristic of these cases that the name *La Cyanose Congènitale Paroxystique* has been proposed. Loss of consciousness may occur during the attack and the heart may stop beating, or death may supervene. Three typical cases were reported by Hall in infants, all of whom died during the attack, and others by Sanders, Carmichael, Luys, and Bommer.[1] In the latter (aged sixteen weeks) the cyanosis was transient, coming on only during the attacks, which came on especially during feeding, and recurred at last so frequently that the child failed for lack of nourishment; during the attacks the breathing stopped suddenly and deep cyanosis developed, lasting two to four minutes; it passed off entirely as the breath returned, in the interval the color being normal. This is very suggestive of an admixture of venous with arterial blood as the cause of temporary cyanosis, the pressure becoming higher in the pulmonary artery and lower in the aorta during the act of suckling.

In older subjects cardiac seizures of various sorts may replace these suffocative dyspnœic attacks. Paroxysms of extreme tachycardia (pulse 200), with dyspnœa and bloody expectoration, lasting for some

[1] *Freiburg Thesis*, 1900.

hours, and recurring every few months, are described in a man aged thirty-six years, with dyspnœa and palpitation on exertion for years, but no cyanosis (Bommer). Hale White reports repeated angina-like attacks, in one of which death occurred, in a man aged fifty-three years, with a patent duct the size of the anterior tibial artery, but no hypertrophy of the heart or disease of this or of the aorta.

Epistaxis, hematemesis, and hemorrhages from other mucous surfaces are not uncommon (Almagro, Carmichael, Darier, Duroziez). Unless death occurs from some intercurrent condition, as malignant endocarditis or endarteritis, the patients usually die with failing compensation, and dyspnœa is a remarkably constant feature. Sudden death occurred in eleven cases in our series; in six during dyspnœic attacks, in three, those by Reid, Crouzet and Chessman, without apparent cause, in the case by Mead from rupture of the heart and in that by Durno Brown from rupture of the pulmonary aneurism above described.

Physical Signs are almost invariably present, and are usually characteristic in older patients. In infants they are practically indistinguishable from those produced by auricular and ventricular septal defects. This is because the patent duct is at first a straight canal, which does not allow of the passage of a large volume of fluid and because in the absence of dilatation of the pulmonary artery there is less sound produced by the impinging of currents in this situation. Among our 64 cases physical signs were absent in only 8 cases. Absence of physical signs in the case of Walsham, quoted by Vierordt in this connection, must be pronounced doubtful, for the specimen came from the dissecting-room with an indefinite note that cyanosis and pericardial murmurs existed. A negative finding in the cases by Luys and Duroziez was also disputed by Almagro.

The distinctive physical signs (which develop as life proceeds), as well as the absence or late appearance of cyanosis, depend, as Gerhardt pointed out, on the fact that a patent duct of long standing usually has a short, wide lumen through which during systole blood flows freely *from* the aorta into the pulmonary artery, which dilates accordingly and becomes, with the ductus itself, the chief seat of whatever vibration or murmur the abnormal current may produce; the right ventricle behind it usually undergoes hypertrophy and dilatation as well. Gerhardt described as characteristic a visible systolic pulsation in the second left interspace (indicating the forcible closure of the pulmonary valves), an increased area of cardiac dulness, especially to the right, and a narrow zone of dulness 3 to 4 cm. wide (corresponding, he believed, to the dilated pulmonary artery) lying at the base of the heart, along the left sternal border from the third to the second or first rib, and extending a little way over the first piece of the sternum. This "ribbon-shaped" dulness has been noted by many other observers, and has recently been strikingly confirmed in a number of cases in which Gerhardt's dull area, with characteristic murmur or thrill localized over it, has been found by the *x*-ray to correspond with a pulsating shadow lying above the base of the heart, which was evidently from its size and position the dilated pulmonary artery. In Bittorf's case this shadow was seen, when looked

at from the side, to be the size of a walnut and to pulsate a little later than the heart and synchronously with the aorta. In Arnheim's case the *x*-rays showed, besides enormous hypertrophy of both sides of the heart, which occupied nearly the whole left thorax, the greatly enlarged shadow of the pulmonary artery placed above the cardiac shadow "like a cap," and numerous tortuous dilated vessels, indicating an extensive collateral circulation and a probable coexisting coarctation of the aorta. In the cases reported by Schrötter, Mead, and Hamilton and Abbott, the *x*-ray cap, and Gerhardt's dulness, were found at autopsy to correspond with the dilated pulmonary artery.

When cardiac hypertrophy is marked, precordial bulging, diffuse pulsation, and other evidences will be present. An increased area of cardiac dulness, especially to the right, while usual, is not invariable, for the left ventricle may be hypertrophied in excess of the right (Murray's case), or in rare instances there may be no cardiac hypertrophy at all (Drasche's case).

A *thrill*, usually systolic, but sometimes continuous through the cardiac cycle, is fairly frequent, and was present in 17 of the 64 cases. It may be diffuse over the precordium, but is usually localized to the neighborhood of the second left interspace, in the region described above as Gerhardt's dull area, or at least is of maximum intensity here. Its transmission obliquely upward below the clavicle (along the course of the pulmonary artery) is said to be pathognomonic.

The auscultatory phenomena are the most important and constant. In infants a harsh systolic murmur with more or less of the above localization is the rule, but in adults a loud murmur is nearly always produced, which is characterized by almost all observers as peculiar, and is variously described as harsh, musical, scraping, scratching, humming, churning, rushing, rolling, and only rarely as blowing. Müller compares it in his case to "rolling thunder," and says that two different listeners likened it independently to the noise made by a train in passing through a tunnel, and Thayer described it in Mead's case as a "machinery murmur." In rhythm several different types may be made out: (1) The murmur is frequently systolic (as in the cases by Murray, Hale White, Simmons, and Bittorf). (2) It may begin with systole, but continue into and through diastole, either as a continuous hum (Chessman's case), or with a systolic rise (Bommer), or with a rhythmic systolic, and diastolic accentuation. Gibson[1] describes as pathognomonic a continuous, rushing murmur which "begins distinctly after the first sound, accompanies the latter part of that sound, occupies the first pause, accompanies the second sound (which may be accentuated in the pulmonary area, or doubled), and finally dies away during the long pause." (3) Sometimes, as in Drasche's case, two independent murmurs are heard at the pulmonary area, the loud, peculiar, systolic one, and a low, short, diastolic, indicating a slight regurgitation into the aorta during the pause. (4) More rarely the murmur is diastolic in rhythm, as in Fagge's case, in which a diastolic murmur, musical and of a wavy

[1] *Medical Press and Circular*, May 30, 1906.

character, was localized to the pulmonary cartilage. The point of maximum intensity is usually in the second or third left interspace, and it is often heard very loudly in the first left interspace below the clavicle and over the first part of the sternum and in the back to the left of the third and fourth dorsal vertebræ, and in the left suprascapular region. In Franck's case and in one by Gillet, the murmur was only heard posteriorly in this situation, and not in front at all. It is transmitted over the left ventricle, and its systolic element often is audible over the carotids, sometimes more distinctly over the left than over the right (Gerhardt). It may diminish abruptly below the third left costal cartilage. In this series of 64 cases, among the 18 cases in infants, in 8 a systolic, and in 1 a continuous murmur was present. Among the 46 adults, in 19 cases the murmur was systolic, in 9 "double" and in 14 it was the continuous "harsh," "rumbling," "rolling," "churning," "humming" murmur usually with systolic accentuation, described by the earliest students of this subject as characteristic, and which Gibson rightly described as pathognomonic.

Franck mentions, as of diagnostic value, an inspiratory accentuation and an expiratory diminution both of the characteristic murmur and of the radial pulse (pulsus paradoxus), which they explain by saying that during respiration the pressure in the thorax is lowered, so that more blood can enter the pulmonary artery then than during expiration, and this will lead to a smaller pulse wave from the aorta, to a larger current through the canal, and a correspondingly louder murmur.

The second pulmonary sound is frequently much accentuated, and this is very important as distinguishing patency of the duct from pulmonary stenosis with somewhat similar localization of murmur or thrill. On the other hand, in some cases it may be weak or even inaudible.

In the cases by Schrötter and Mead *paralysis of the left recurrent laryngeal nerve* was present, due to pressure upon the nerve by the enlarged patent duct. Schrötter based a correct diagnosis on this feature. The nerve was degenerated on microscopic examination.

The physical signs are very often obscured by those of other lesions, as malignant endocarditis or arteritis, chronic valvular disease, or other cardiac anomalies so commonly associated. The peculiar character of the murmur, its more or less prolonged rhythm, its localization, and that of the thrill when present, high up toward the left infraclavicular region, with the results of *x*-ray examination, remain, even in these complicated cases, of the first diagnostic value. Patent duct must be diagnosed also from perforation of the aorta and pulmonary artery just above the semilunar valves, whether of inflammatory or congenital origin. Brocq[1] gives a long series of cases of both types.

So-called aneurisms of the ductus Botalli give rise to no physical signs, being of small size and usually occluded by thrombus. They are generally said to be of little clinical significance, but death from rupture of their walls has been reported and embolism from the thrombus within may lead to a fatal result.

[1] *Rev. de Méd.*, 1886, vi, 786.

So-called Aneurisms of the Ductus Botalli.—This term is used in the literature with a rather irregular application to denote a dilatation in whole or in part of a persistently patent duct. That the cases are not aneurisms in the strict sense is inferred by most writers. Rokitansky uses the qualifying word "so-called." Gruner says that arterial dilatation would often be a better word, as there is usually no change in the vessel wall, and he draws attention to the fact that in the usual bean-shaped form the constriction at either end makes the ductus appear larger to the eye than it really is. Klotz has suggested that, as in his injection experiments the duct is seen to be much larger at birth when distended with fluid than when contracted at the autopsy, many of these small, so-called aneurisms, measuring less than 1 cm. in their greatest diameter, are really not even a dilatation, but are a simple distension of a patent duct to its full capacity by the coagulum within. Again, a further confusion exists in that the term is applied more widely by some writers than by others. Nevertheless, the cases recorded form a fairly well-defined group, which, from their rarity and from the fact that the duct is usually occluded by thrombus, are chiefly of pathological interest, although their occasional rupture, and also the risk of embolism from the thrombus within, increase their clinical significance. The first cases reported were by Billard, Thore, and other French writers; Rokitansky followed with his monograph in 1852, and Virchow in 1856; full studies of the literature with original cases are to be found in the theses of Westhoff,[1] and Gruner.[2]

In what may be taken as the classical form (which is that described by Rokitansky) the ductus forms a spherical or ovoid tumor larger at the middle than at either end, but smallest toward the pulmonary artery, with which, as well as with the aorta, it communicates, filled with old or recent thrombus, and varying in size from a "cherry stone" (Billard) to a "hazel nut" (Thore), or even a walnut (Hebb, Binzer). In Hebb's case,[3] in a man aged forty years, an aneurism the size of a small walnut, filled with old clot, lay in the position of the duct, communicating with the aorta by an orifice one-eighth of an inch in diameter, and abutting against the obliterated left pulmonary artery and left bronchus. All the cases recorded are in infants excepting that by Hebb.

In Thoma's[4] patient, aged twenty-six years, the aorta, from the isthmus downward for about 4 cm., was dilated in the form of a spindle, was lined by atheromatous plaques, and on its right wall opposite the left subclavian artery was a saccular aneurism, in the floor of which lay a small hole representing the lumen of the greatly shortened ductus leading into the pulmonary artery, which was here firmly adherent to the aorta. Microscopic examination showed this aneurism not derived from an expansion of the aortic end of the ductus, but to be a bulging of the aortic wall, which the writer thought was pulled to the right by the action of the contracted ductus. Rokitansky's 5 cases of funnel-shaped patency were explained by Thoma in the same way, and a special form of "traction aneurism of the infantile aorta" was thus established by

[1] *Göttingen Diss.*, 1873 (quoted by Gruner and Voss).
[2] *Freiburg Diss.*, 1904.
[3] *Trans. Path. Soc.*, London, 1893, xliv, 45.
[4] *Virchows Archiv*, 1890, Bd. 122, p. 535.

him. In Wagener's 3 cases, aged respectively thirty-eight, forty-two, and twenty-three years, the duct formed a distinct canal with a small lumen open on the side of the aorta, where the orifice lay in the floor of a hollow in the wall of this vessel, and was sheltered by a distinct fold of aortic intima projecting downward from above while the pulmonary end was closed in by a thin membrane, which bulged into the pulmonary artery. Mycotic aneurism of the patent duct of the dissecting form has been described by Buhl.

Absence of the Ductus.—Absence of the ductus may occur, and is usually associated with hypoplasia and shortening, sometimes with atresia, of the pulmonary artery. It is explained as due to a primary failure of development of the sixth left branchial arch (which persists as the ductus), the stenosis of the pulmonary being secondary. In these cases a septal defect is present, through which the aërated blood passes from the right heart to the aorta.

Anomalous Course.—Multiple origin is reported by Peacock in a case of pulmonary stenosis, two small trunks arising at the site of the normal ductus and passing, the smaller into the left, the larger (which was cut short) apparently into the right pulmonary artery. In several cases the canal has opened into the left subclavian. In one case, of right aortic arch, the duct entered the descending aorta below the right subclavian and itself gave off the left subclavian artery.

COARCTATION OF THE AORTA.

This term applies to a well-recognized group of cases in which there is a narrowing or stenosis, amounting sometimes to a complete obliteration, of the descending arch at, or immediately below, the so-called isthmus of the aorta, which is that part of this vessel lying between the left subclavian artery and the insertion of the ductus arteriosus. During the period of fetal circulation this segment is comparatively little used, and at birth is usually observed to be of slightly smaller lumen than the adjacent portions of the aorta, the difference soon disappearing under normal conditions. Thérémin states, as a result of his measurements of the normal infant heart, that in 80 per cent. a slight diminution in diameter exists in the isthmus during the first three months of postnatal life, after which a calibre uniform with the remainder of the arch is attained; and that in some 6 per cent. a slight difference remains throughout life which he does not consider abnormal unless it amounts to more than 2 mm. Bonnett classed as anomalous those cases in which the difference was about 3 mm.

Two distinct groups of cases are understood under the term. (*a*) A diffuse narrowing of the aorta at the isthmus (Bonnet's infantile type). In some of these cases in which the stenosis is marked, the circulation in the lower part of the body is maintained by a large patent ductus arteriosus through which *the descending aorta appears to be a direct continuation of the pulmonary artery.* Such cases, being essentially the same in origin as coarctation, may be included with it. (*b*) A more or less abrupt constriction of the aorta at or near the insertion of the ductus arteriosus (Bonnet's adult type). Here, where coarctation is marked and has

lasted some time, the establishment of an extensive collateral circulation frequently completes the picture and lends distinctive features to what is otherwise an obscure lesion.

Relative Frequency.—The figures in the literature are somewhat misleading, for curiously little account is taken of its occurrence by many workers, and therefore the lesser degrees of coarctation are probably often overlooked in the postmortem room, and cases with well-marked vascular changes may escape diagnosis at the bedside. On the other hand, this subject has been so carefully worked over and brought up to date by successive writers, that its statistics are clearer and more accessible than is the case perhaps in any other chapter of congenital cardiac disease. Very probably, therefore, the 212 cases enumerated here are not far from being the full number recorded, whereas the total number of pulmonary stenosis or of septal defect (which anomalies have not been subjected, at least of recent years, to such careful repeated statistical analysis) must be much higher than that given by any author. For this reason Vierordt's statement that coarctation ranks next in frequency to pulmonary stenosis is probably placing the incidence too high. A truer estimate may perhaps be gathered from the fact that among 205 cardiac anomalies recorded in the *Transactions*, there are 22 of stenosis or obliteration of the aorta at the isthmus and 2 of entire absence of the aortic trunk between the left subclavian and the ductus, against 91 of pulmonary stenosis and 165 defects of the interventricular septum.

The first case was reported by Paris in 1789. Craigie collected 10 from the literature in 1841, von Leeuwen 18 in 1850, Rokitansky 26 in 1852, and Peacock 46 cases in 1866. Barié,[1] in 1885, gave a review of 89 cases, in which he published the series of the above authors, with others from the literature. The fact that 6 of these are without autopsy findings reduces the number of Barié's cases for statistical purposes to 83. Schichhold, in 1897, added 30 to these, and Vierordt, in 1898, brought the number of recorded cases to 126. In 1903, Bonnet[2] published an article analyzing Barié's findings, and adding to these a synopsis of 77 additional cases which include the series of Schichhold and Vierordt, make, together with the 83 cases collected by Barié, a total of 160, of which 55 are in infants and 105 in adults. In addition to Bonnet's 160, the writer[3] has collected records of 52 cases not included by the

[1] *Révue de Médecine*, 1886, vi, 501. [2] *Révue de Médecine*, 1903.

[3] Of these 52, 15 are from a series of 18 cases collected by Fawcett from *Guy's Hospital Reports* and published in 1902; 12 are from the *Transactions* reported by Chevers (vol. i, p. 55), Rees (vol. ii, p. 203), Peacock (vol. vii, p. 83), Lees (vol. xxi, p. 58), Wilkes (vol. xi, p. 57), Smith (vol. i, p. 52), Barlow (vol. xxvii, p. 41), of coarctation in infants, and by Peacock (vol. xii, p. 38), Finlay (vol. xxx, p. 262), King (vol. xxiii, p. 83), Habershon (vol. xxxix, p. 71), Mackenzie (vol. xxx, p. 66), in adults. The remainder are reported by Preisz (*Jahrb. f. Kinderheilk.*, xxxiii, p. 140), Lawrence and Nabarro, Hektoen, Dick (*Proc. Clin. Path. Society*, May 9, 1904), Osler (*Montreal Gen. Hosp. Rep.*, P. M. No. 252), Pansch, (*Giessen Thesis*, 1905) in infants, and by Pappenheimer (*Proceedings New York Path. Soc.*, May, 1905, January, 1906, p. 177, October, 1906), Variot, Carmichael, one in *St. Bartholomew's Hosp. Rep.*, vol. i, series I, one in the Museum of Toronto University, in adults, Mönckeberg (2 cases) (*Deut. Path. Gesell.*, 1907, xi, 267), Moon (*Lancet*, June 8, 1912), Rokitansky (3 cases) (*Krank der Arterien*, 1862, Obs. 21), Sella (2 cases) (*Zieg. Beit.*, 1910, lxix, 501), Strassner (*Deut. Arch. f. klin. Med.*, 1909, lix, 349), Wadstein, 1897 (quoted by Sella), Oberndorfer (*Verh. deut. Path. Gesell.*, January, 1910), MacCallum.

above authors, 15 of which are in infants and 37 in adults, making a total of 212 cases, of which 70 are in the newly born, and 142 in patients over one year.

Pathogenesis.—The proximity of the stenosis to the insertion of the duct in the aorta suggests that the part which this vessel takes in the circulation, or the changes which go on in its form and tissues during its closure after birth, have an essential bearing on the production of coarctation. Rokitansky (1852) assumed *in all cases,* as the essential condition, a persistence of the isthmus and a consequent weakening of its walls so that they yielded, in a way the healthy aorta would not do, to the traction exerted upon them by the contraction of the duct in its obliteration. Skoda (1855), made the interesting suggestion that in those cases in which the isthmus was not obliterated at birth as a true anomaly brought about by an atrophy of the corresponding embryonic aortic arch, the tissue of the duct had extended into the wall of the aorta, which thus contracted as part of the same process by which the canal itself is obliterated, and Brunner (1888) supposed the transplantation of free portions of the ductus tissue into the adjacent wall of the aorta to occur, rather than its direct extension.

Bonnet gave the most satisfactory contribution to the subject. He divides the cases of coarctation into two types, according as these occur in the newly born or in adults, for each of which he claims a different etiology:

1. The form described by him as that usually seen in the newly born is a diffuse narrowing of the isthmus, and is assumed to be of developmental origin; it is frequently associated with grave anomalies; in it the ductus arteriosus is often patent. The cases in this type fall again into two classes as regards their etiology: (*a*) When, as in the majority of cases, the stenosis is moderate in degree, it is explained as a persistence of the isthmus at birth, an arrested fetal condition in which this segment fails to attain its normal calibre, and the cause of which is to be sought at or shortly before birth in a simple weakening of the vessel wall, the result probably of a lowered state of general nutrition. Thus Thérémin observed that in the case of his so-called normal infant hearts in which the isthmus was abnormally narrowed at birth, there was a history of premature delivery or of general weakness, and, conversely, that in 50 per cent. of infants born before term or weakly, marked narrowing was present. (*b*) Those rare cases of the infantile type, on the other hand, with an extreme degree of diffuse stenosis, or in which the isthmus is reduced to an atrophic cord, are probably to be explained, as are also the few recorded cases in which there is a complete absence of the aorta between the left subclavian and the entrance of the ductus, as a failure of development in early embryonic life of that part of the fourth left branchial arch which corresponds to the isthmus of the aorta.

2. Bonnet places in a second class as the adult type those cases seen usually after infancy is passed, in which the coarctation consists of a more or less abrupt constriction of the aorta at or near, often a little below, the insertion of the ductus. This condition, which is never seen in the fetus, nor at birth before the closure of the ductus has begun, is,

he thinks, not of developmental origin, but is to be explained on Skoda's theory of an extension of the peculiar tissue of the duct into the adjacent wall of the aorta, which thus contracts after birth along with the contraction of the arterial canal. As the malposed tissue is scanty and tends to be of a width corresponding to that of the narrow ductus, its contraction will have the effect of a narrow ligature or cord. These cases differ from those of the infantile type not only in the character of the stenosis, but also in that an extensive collateral circulation, giving rise to marked physical signs, usually develops, while serious anomalies are generally absent, this last fact arguing in favor of its postnatal origin. The ductus arteriosus may remain patent, but is usually obliterated.

Associated Anomalies.—The distinction drawn by Bonnet between two types of cases offers a new and significant suggestion. A statistical analysis, on the basis of this division, of the 212 cases available gives interesting confirmation of this statement, and points to a radical difference in the etiology of the two groups. The following figures include as *minor* anomalies occurring chiefly in the adult type, anomalous semilunar cusps, irregular origin of the vessels from the arch, patency of the foramen ovale or duct, persistent left superior cava; and as *grave* anomalies, septal defects, transposition of the great trunks, congenital stenosis, etc.

Associated Anomalies in Coarctation in the Newly Born (70 Cases).

Series.	Absent.	Minor.	Grave.
Barié	0	3	3
Bonnet	13	11	25
New cases	0	3	12
Total	13	17	40

In Cases Over One Year ("Adult Type") (142 Cases).

Series.	Absent.	Minor.	Grave.
Barié	57	19	1
Bonnet	15	11	2
New cases	8	16	8
Total	80	46	11

Thus among the 70 cases of stenosis in the newly born (dying under one year), in only 13 instances was there no other defect associated; minor defects were present in 17 and in 40 cases grave anomalies coexisted. That is to say, there is frequently associated with the graver cardiac anomalies that form of coarctation which may reasonably be ascribed to a simple arrest of development in later fetal life, and which is due probably to the depressing influences that led to the associated defects, or possibly in some instances to the disturbed circulation that results from the combined anomaly.

On the other hand, among the 142 cases in patients over one year (adult type), other anomalies were absent in 80 instances, minor defects were present in 46, and grave anomalies were associated in only 11 cases; moreover, 7 of these 11 had not the characteristic sharp constriction seen in the great majority of these cases, but were apparently a persis-

tence of the infantile type; for in 3 (Chiari, Houel, MacKenzie) the pulmonary formed the descending aorta through a large patent duct, and the 4 others were in children of two to five years in whom the isthmus was simply diffusely narrowed. Transposition occurred in only 1 (Fawcett), a child aged two years and nine months, with a stenosis apparently of the infantile type. Persistent left superior cava was noted only once (Bonnet).

Equally significant with this rarity of grave anomalies in the adult type of coarctation, suggestive, too, of some etiological factor as yet unknown, is the frequent association in this type of a certain set of minor defects in the structures connected with the aortic arch, namely, irregularities in the origin of the great vessels, absence of the ductus (3 cases), double ductus (Hammernjk), and especially *anomalies of the aortic cusps*, which last are relatively so common as to seem to place their combination beyond the range of coincidence. Thus the *aortic valve was bicuspid* (in itself a rare anomaly) *in* 15 *instances;* its segments were increased to four with fusion of two of these in one (Fawcett); in one instance (Babington) a small supernumerary cusp had formed on the aortic wall above the others; in two there was subaortic stenosis, in the form of a membranous band below the cusps, and in one there was sub-aortic stenosis and a band of fibrosis with contraction above the aortic cusps.

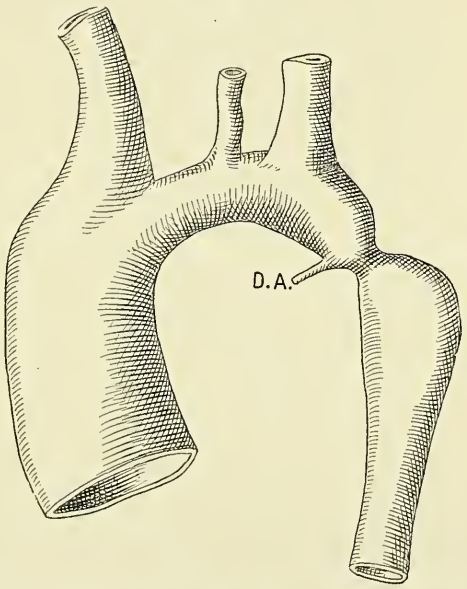
In the infantile type, on the other hand, amid so many grave anomalies, bicuspid aortic valves occurred only twice.

Pathology.—1. The diffuse stenosis of the isthmus usually observed in infancy and always present during the period of the fetal circulation (Klotz), is seen occasionally, but rarely, in later life. It is usually limited below by the ductus, and may begin above as a gradual diminution of the arch, or abruptly at the origin of the left subclavian artery, or, in a few instances, in which the isthmus itself appears to be placed higher up than usual, at the innominate or left carotid artery. The ascending aorta may be dilated or of normal calibre, and below the stenosis the vessel may remain smaller than usual, may return to its full size, or in cases where its descending portion is supplied by a patent duct, be much dilated. The lining of the stenosed area is usually smooth and healthy. In degree it may vary from a mere shade below the normal to a lumen of 1 to 2 mm. in diameter, or be represented in rare instances by a fibrous obliterated cord. Among the total 212 cases, the pulmonary artery formed the descending aorta through a large patent duct in 15 instances, in all of which marked coarctation of the infantile type existed.

2. *Adult Type.*—A very different anatomical character and a much wider variation are presented. In typical cases the aorta is abruptly constricted at the level of, or a little above, or, most frequently, directly below the insertion of the ductus, as though by a tight ligature or cord, the groove thus formed being usually deepest on the convex side of the arch, which appears deeply indented as though cut through in V-shaped manner (Fig. 39). The aorta on either side usually diminishes rapidly toward the stenosis in an hour-glass or funnel-shaped manner, or it may be dilated on either side, giving a sausage-like effect (Bradley). Viewed

from within, the inner surface of the constriction usually presents a projecting ridge or fold corresponding to the zone of constriction without. This may be so marked as to form a distinct septum bridging across the lumen, sometimes obliterating it entirely or leaving a small central circular or triangular lumen, the constriction involving all the coats of the vessel or only its inner ones, the adventitia passing outside of it like a bridge. In other cases the stenosis may occupy a wide area and appear from without like an annular band. Kriejk describes it in his case as a sort of resistant ring, enclosing the aorta like a cuff parallel to the axis of the vessel, and Mannaberg as a solid segment 0.5 cm. long just below the insertion of the duct. The lumen varies through all grades of stenosis down to one just admitting a bristle. In 25 cases of the 142 it was entirely obliterated, in some instances by a septum or diaphragm formed within, but more frequently by the elongated annular form of constriction.

FIG. 39

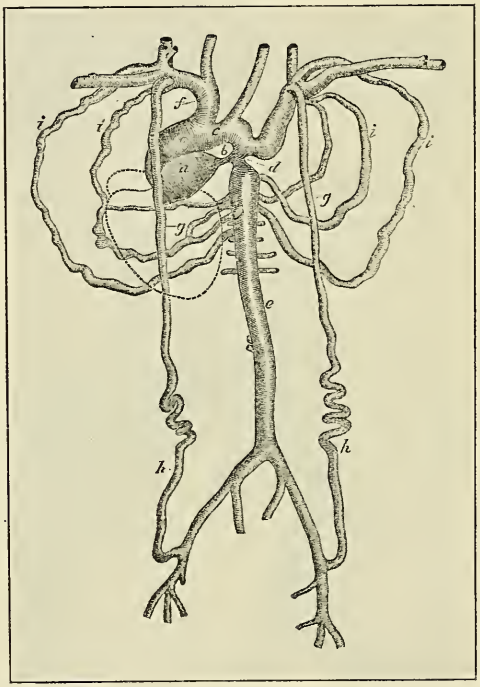


Coarctation of the aorta in a woman aged twenty-seven years. Stenosis beginning just beyond the origin of the innominate artery; sharp constriction immediately below the insertion of the obliterated ductus (*D. A.*). (Reproduced from Bonnet's article, Revue de Médecine, 1903.)

The aorta may be of normal calibre above and below the stenosis, or it may be slightly narrowed at its origin and dilated for a short distance up. The diminution in calibre not infrequently begins at the innominate or left subclavian artery, and in a certain percentage of cases is followed by a dilatation, below which again the characteristic tight constriction near the duct takes place; the effect being that of a *double stenosis*. The aorta immediately below the stenosis is often widely dilated at the seat of origin of the intercostals. *Hypoplasia* of the vessel in its whole length existed in the cases of Hale White, Riegel and Mönckeberg (2 cases). In other cases the aortic walls, otherwise healthy,

are noted as abnormally thin. The aorta may be smooth and healthy in its whole course, as in the cases reported by Brunner (complete obliteration), Cruveilhier, Almagro, Purser, and in the original one by Paris, or there may be extensive atheroma with calcification at the seat of stenosis, above or below it, or throughout the whole aorta. This was present in 39 of the 142 cases, in 9 of which it was definitely stated to be at the seat of stenosis, in 9 localized in the ascending aorta, in 4 localized below the stenosis, and in 7 diffuse throughout the aorta.

Fig. 40



Diagrammatic representation of collateral circulation in a case of coarctation of the aorta: *a*, pulmonary artery; *b*, arterial duct; *c*, arch of aorta; *d*, coarctation of aorta; *e*, descending aorta; *f*, innominate artery; *g*, internal mammary artery; *h*, epigastric artery; *i*, *i*, *i*, *i*, deep-seated arteries of neck and intercostals, forming, together with the internal mammary and epigastric arteries, a collateral circulation with the thoracic and abdominal aorta and internal iliacs. (From Diseases of the Heart and Great Vessels, by W. H. Walshe, London, 1862.)

Rupture of the aorta occurred in 14 cases, in 9 cases at the ascending portion, and in 8 at the seat of stenosis. Aneurism of the arch occurred in 11 instances, and in 8 of these it was of the dissecting form. Sella has made a study of 12 cases of rupture of the aorta, and ascribes its frequent occurrence to the abnormal thinning of the ascending arch, which occurs in many cases of coarctation and which renders the coats more liable to yield under the increased strain.

In most well-marked cases of coarctation of the adult type the blood supply of the lower part of the body is maintained by the development of an extensive *collateral circulation*. The great vessels of the arch are

often enlarged to twice their calibre, and the smaller branches involved are converted into thick, tortuous, dilated trunks. The principal anastomoses are carried on by the superior intercostals, the internal mammaries, and the posterior scapular branches of the transversalis colli *above*, with the first four aortic intercostals, the phrenic and superficial and deep epigastrics *below* the stenosis.

Some evidence of collateral circulation was present in 66 of the 142 cases of the adult type. The particular branches involved and the degree of dilatation vary greatly even in cases of extreme constriction. In 3 instances out of the 142 (Barié, Pic and Bonnamour, and Dubreuil) it was expressly stated to be absent; in most of the remainder the collateral circulation was not mentioned, but this does not imply that it was always absent entirely, as minor alterations in the peripheral vessels are easily overlooked.

The *ductus arteriosus* was patent in 13 of the 142 adult cases. In some instances the ligamentum arteriosum is described as "solidified" or much thickened as though by inflammatory action. Among the 70 cases in infants under one year the ductus was patent 51 times.

Marked *hypertrophy with dilatation of the heart* is rare in infants, but occurs in the majority of the older cases, being noted in 87 out of the 142. It is stated by most authors to be the direct result of the obstruction in the course of the descending arch, but the relation of the two conditions is rendered uncertain by the frequent association of chronic valvular disease, which must be a factor in the hypertrophy. Moreover, a few cases are recorded (*e. g.*, Reynaud's aged ninety-two,) in which, with marked constriction or, even, as in Brunner's case, an obliteration at the insertion of the duct, the heart has remained normal throughout life. This was stated to be the case in 10 of the 142 cases. Although this is a small percentage, it proves that new channels provided for the blood by the dilated collaterals may be sufficient to carry on the circulation without increasing the work of the heart. In Dumontpallier's patient, aged thirty-nine years, in whom the stenosis was produced by a septum with triangular central opening, 13 mm. in diameter, and the heart was not hypertrophied, the collateral circulation was carried on chiefly by the aortic intercostals and the vessels from the subclavian, the anastomosis between the internal mammary and the epigastrics being little developed.

On the other hand, an analysis of the 87 cases with hypertrophy shows that while 50 were complicated with chronic valvular lesions or other cardiac defects, in the remaining 38 no cause was present except the coarctation itself. Of the latter, there were 38 cases of hypertrophy without any assignable cause except the coarctation, hypertrophy was confined to the left ventricle in 9, and involved the whole heart in 30, of which latter the left ventricle especially was enlarged in 9. An interesting point is that in 20 of the 38, the collateral circulation was either stated to be absent or was not mentioned, and in 6 more it was not much developed, the only sign noted being a dilatation of the great vessels of the arch. In the 12 remaining cases a collateral circulation had developed, but in 4 of these the cardiac hypertrophy was only slight.

These facts argue that even in extreme degrees of constriction the heart may remain normal in the presence of an adequate collateral circulation, but that when this becomes insufficient, cardiac hypertrophy and dilatation supervene.

Age and Sex.—A remarkable predominance of the adult type of the anomaly in the male sex is noted by all writers. Among 133 of the 142 cases over one year, 92 were in males, and 41 in females.

That the stenosis does not necessarily interfere with the duration of life is proved by the fact that 9 patients died in the sixth and 9 in the seventh decade, while one (Reynaud's) lived to the age of 92. More than half of the remainder, however (63 cases), died between the ages of twenty and forty years; indicating that, in the anomalous conditions of the circulation that prevail, the system is not, as a rule, equal to the full demands of the stress of normal existence.

In the 142 cases over one year death occurred as follows:

	Cases.
1 to 5 years	7
5 to 10 "	4
10 to 15 "	4
15 to 20 "	17
20 to 30 "	37
30 to 40 "	26
40 to 50 "	16
50 to 60 "	9
60 to 70 "	9
Over 70 "	1
Adults (exact age not mentioned)	12

Symptoms and Course.—Coarctation in infants is of little clinical significance, except in so far as it may complicate other grave anomalies. In the adult type it is a condition of the greatest interest and importance. Symptoms when present may be distinguished as those associated with the lesion and those of the cardiac insufficiency which frequently supervenes. As characteristic of the overtaxing of the altered circulation, in which the blood supply to the head and upper extremities is freer than that to the lower part of the body, may be mentioned; violent pulsations (Flaherty's case), plethora with sleeplessness and continuous buzzing in the ears (Legrand), violent headaches (Hammernjk), lividity of the face (Chevers, Purser, Kjellberg), suffusion of the head and neck (Moore), epistaxis and hemoptysis (Flint); in Dubreuil's case, a vascular surcharge of the head and chest contrasted with an atony of the subdiaphragmatic viscera; in that of Redenbacher, a boy aged seven years, with a stenosis at the isthmus admitting a crow-quill, and extensive collateral circulation, the development of the head and upper extremities was in advance of that of the lower part of the body. Severe thoracic, epigastric, or abdominal pain and vomiting of long standing (Roemer's case), or pains in the back or lower extremities (Lebert) occur, and may perhaps be due to the local effect of the constipation. Of significance is Muriel's report of a man aged twenty-five years, who was always weakly, and who developed severe pains in the back and symptoms of aneurism of one of the large vessels of the chest; post-

mortem a dense mass of enlarged glands the size of a hen's egg was found adherent to the aorta at the point of its constriction; it had eroded the dorsal vertebræ. Precordial pain and oppression, dyspnœa, and severe palpitation indicate the cardiac strain. Cyanosis is extremely rare except as a terminal event; in only 2 uncomplicated cases in the whole series (Almagro and Carmichael), in both of which the ductus was patent, was a true congenital cyanosis present throughout life. Lack of development was noted three times, delayed menses once. Many end with a stage of failing compensation, which, in those not complicated by chronic valvular disease, is usually identical with that of mitral incompetence.

Symptoms are (*a*) absent, (*b*) late in developing, or (*c*) present throughout life. (*a*) In some of the most well-marked cases of constriction or even obliteration at the isthmus, symptoms are absent throughout life. The condition may be quite latent, and constitute, in Barié's words, a "*surprise d'amphithéatre*" at the autopsy, death occurring from some intercurrent, independent disease. Thus Crisp describes a chance finding of a stenosis admitting a goose-quill in a soldier aged forty-eight years, who had been in excellent health and had died accidentally, and Scheiber complete obliteration of the descending aorta in a man aged forty-one years, dying of pneumonia, who showed no signs of heart disease. In these latent cases sudden death may occur. In most instances a rupture of the heart or aorta is found (Lüttich, Barker, Wise, Legg, and others). Death took place without previous warning or symptoms in 16 of the 142 cases, constituting an event of sufficient frequency to have an important medicolegal bearing.

(*b*) A large proportion of the cases are in able-bodied, vigorous men, in whom the lesion long remains latent, symptoms developing as the altered circulation becomes overtaxed, or on the intercurrence of some complicating condition, especially endocarditis. Not infrequently, symptoms developing late in life are entirely cardiac in character, cases otherwise latent terminating with a stage of failing compensation which may be due to the lesion itself, or to the chronic valvular disease so often associated.

(*c*) In a few instances only, symptoms of some obstruction in the cardiovascular system are present throughout life. Quinquaud's patient, a youth aged nineteen years, suffered from infancy with intense palpitation and violent dyspnœa, so that he could not join in play, and œdema of the extremities developed shortly before death, which occurred suddenly. Erman's patient was weakly and had always suffered from dyspnœa. Death took place at 19, after seven and a half months of failing compensation. Lebert's patient, aged twenty-two years, had long had epistaxis and dyspnœa, and developed cardiac symptoms in the last two years.

Physical Signs.—These bear no constant relation to the symptoms, but may be present where these are quite lacking. Nor, on the other hand, do they correspond to the degree of the constriction, nor to the extent of the collateral circulation, both of which may be developed to an extreme degree without yielding any evidence of their presence.

The most marked signs appear to be produced in association with chronic valvular disease or bicuspid aortic valves, or with the relative mitral incompetency of the later stages of the cardiac dilatation that frequently supervenes, in which cases the murmurs formed in the heart may be propagated along the vessels. The signs peculiar to the lesion may best be studied in uncomplicated cases. They are both vascular and cardiac, and are present in varying degrees and combinations in the majority of cases.

Vascular.—These depend chiefly upon the inequality of the circulation in the upper and lower halves of the body, and upon the unusual appearances presented by the dilated collaterals. In well-marked cases the vessels of the upper half of the trunk may be seen pulsating, the subclavians, as a rule, more markedly than the carotids; and pulsation may be traced in many cases along the abnormally dilated and tortuous vessels occupying the course of the internal mammaries on either side of the sternum, or the posterior intercostal or scapular arteries behind. In Libman's patient there was a varicose mass beneath the skin of the abdomen; in Flint's, both supraspinous fossæ were occupied by a network of tortuous pulsating vessels; in Leudet's, small arterial dilatations extended over the middle of the thorax both in front and behind, and were most marked at the posterior border of the left axilla and in the left supraspinous fossa, where they formed tortuous, thickened vessels, pulsating synchronously with the radials. Along the whole course of these a murmur, usually postsystolic in rhythm, but sometimes systolic or double, may be heard, and a slight thrill may be felt.

The radial pulse is frequently hard and full, and may be unequal on the two sides. The lower extremities may contrast strangely with the upper half of the body in the absence of all visible pulsations. On examination the pulse in the abdominal aorta and femorals is either very weak or absent, while the murmur usually audible on pressing over the femoral with the stethoscope cannot be heard. In Bonnet's case, diagnosed before death, no pulse could be felt in the abdominal aorta or femorals, and an artery pulsating visibly and as large as the radial, over which an intense systolic murmur could be heard, ran downward between the vertebral column and the inner border of the left scapula. On the right side of the column a similar but less strong pulsation could be felt, but no murmur was heard.

Hornung's patient, a man aged twenty-seven years, is an example of an extreme stenosis not producing any symptoms, but with marked physical signs, in whom death occurred suddenly from rupture of the aorta. There was energetic pulsation and a systolic murmur over the carotids and subclavians. At the inner border of the scapular region were sinuous pulsating vessels. The radial pulse was hard and resistant, and there was no pulsation in the abdominal aorta, popliteral, posterior tibial, or pedal arteries. As long ago as 1839, Mercier diagnosed a case in which there were visible pulsations in the intercostals, a marked bruit at the lower angle of the left scapula, and a very weak pulse in the lower extremities, with epistaxis and symptoms of failing compensation for three months before death.

Cardiac.—The heart's action may be tumultuous, with a heaving impulse, and the organ may present evidences of enlargement, particularly of the left ventricle. A precordial thrill was present in only 3 of the cases. The heart sounds may be quite pure, or accompanied by loud murmurs, usually systolic or postsystolic in rhythm. In Hornung's patient a rough murmur was heard at the aortic area, most marked between the left clavicle and the third rib. In Decker's, a woman aged nineteen years, with complete obliteration at the isthmus and no complicating valvular disease, a rasping murmur filling the whole systole was heard at the apex, and could also be traced along the thickened, tortuous, and dilated arteries, among which the superior epigastric, the long thoracic, and the dorsalis scapulæ formed pulsating cords; the heart was hypertrophied.

Diagnosis.—When such symptoms and signs as the above occur together a very distinctive clinical picture may be formed. It must be remembered that they may be entirely absent, or present only in a fragmentary way, such as may awaken suspicion of the reality, yet render a positive diagnosis impossible. The fact that physical signs as well as symptoms usually do not remain stationary, but progress to a more definite development, furnishes the clue by which the presence of the anomaly may best be traced. A pulsation at an abnormal area, or a superficial murmur of unusual site, noted and watched, may lead to a second examination, at which the full development of the condition may be revealed.

Even where symptoms are present, the diagnosis may be very difficult between a constriction of the descending aorta at the isthmus and obstruction of this vessel or its branches by aneurism, or by the pressure of a mediastinal tumor. The absence of any considerable area of dulness, the transmission of the murmur for long distances along the branches of the ascending arch, the remarkable extent to which the collateral circulation is sometimes developed, above all, the results of *x*-ray examination, contribute differential points in favor of coarctation. In perhaps no other pathological condition are more extensive changes compatible with fewer evidences during life. The later stage of cases in which vascular phenomena are lacking and failing compensation develops, may be impossible to distinguish from that of organic insufficiency of the mitral valve.

Termination.—The cases may be divided into three groups: (1) The condition may be latent throughout life and not interfere with its duration in any way. (2) Both in latent cases and in those presenting symptoms during life death may occur suddenly, by asystole, from rupture of the heart or aorta, or from causes unknown. (3) Death may follow a stage of broken compensation, which may be preceded by symptoms characteristic of the lesion, or may develop suddenly in an apparently healthy subject.

HYPOPLASIA OF THE AORTA AND ITS BRANCHES.

Hypoplasia of the aortic system may be described as that condition in which the lumen of the arterial vessels in the greater circulation remains abnormally small and the walls unnaturally thin and elastic. The heart

may also be reduced in size or may undergo a compensatory dilatation and hypertrophy which involves especially the left ventricle, but may extend to the whole organ, and is usually succeeded by a marked degree of secondary dilatation. The subjects are, as a rule, pale individuals of delicate frame, who present signs of retarded development, such as a delayed advent of the signs of puberty. Anomalies of the sexual organs frequently occur. The general health is usually fair until early adolescence, when the condition generally manifests itself after some unusual physical strain has been endured, by the sudden appearance of failing compensation. The course is then progressively downward. In women, who are by natural conditions less exposed to undue muscular exertion than are men, this stage of cardiac insufficiency may not supervene, but the disease may run its course under the guise of a chlorosis. By some observers (Ortner, Hiller) the narrowing of the vessels is thought to predispose to the infectious fevers, and a special group of cases in which death has occurred from typhoid fever is described. It is also seen in young anemic subjects dying of pulmonary tuberculosis.

There has been some debate as to the pathological significance of the condition. Several authors have maintained that the greater elasticity of the walls of the vessels compensates for their smaller calibre, and so prevents undue strain upon the heart. A number of statistical contributions, have, however, demonstrated that hypoplasia of the aorta must be given a place in pathogenesis as one of the special causes of cardiac asystole. The *etiology* is obscure. In some few cases, such as the cachexias of wasting diseases, a true atrophy of the aorta occurs. In the majority some congenital defect, amounting in some instances to a congenital tendency to dwarfism, may be supposed. This view is supported by the frequent association of other anomalies, especially in the generative and circulatory systems.

Typical cases were described by Morgagni in 1761 and by Meckel in 1788. Rokitansky defined the condition in 1838 and commented upon its association in some instances with defects of the external genitalia. Bamberger, in 1843, noted the association of chlorosis with a small aorta. But in general the subject attracted little attention until Virchow, in 1872, published a series of cases illustrating the frequency of a small elastic aorta and a small heart in chlorosis, and suggested an etiological relation between the two conditions. He explained the absence of compensatory hypertrophy of the heart in some cases and its presence in others, as depending upon the degree of diminution of the lumen of the vessels, the volume of the circulating blood, the elasticity of the vessel wall, and the amount of work done by the individual. Ortner, in 1891, dwelt chiefly on the medicolegal aspect of the subject, and emphasized as pathognomonic an absence of the jugular pulsation in the episternal notch in cases in which the upper border of the cardiac dulness is high. Spitzer (1897) attempted by a study of the recorded material to place the condition on a more definite clinical basis. He pointed out that while the cases usually terminate with failing compensation, this resembles the end stages of chronic valvular disease only in a general way, that the symptoms are in general those of a cardiac overstrain due to

muscular fatigue, and have a progressive tendency to grow worse; that during the stage of broken compensation the cardiac dulness is usually much enlarged, and that the sounds are generally clear, with marked pulmonary accentuation, although occasionally accompanied by murmurs. Like Virchow, he noted as characteristic a remarkable *pallor*, but he ascribed it not to a diminution of the hemoglobin, which he found usually 90 to 100 per cent., but to the reduction in size of the vessels through which a smaller quantity of blood coursed beneath the skin.

Burke[1] (1901) gave a historical review of the subject and a full account of all the cases on record. He divided the material into four groups:

(1) Hypoplasia of the aorta in the so-called blood diseases, as chlorosis, pernicious anemia, hemophilia; (2) hypoplasia in association with infectious diseases, considered as predisposing to these or tending to their fatal termination; (3) hypoplasia with general dystrophies, as acromegaly; (4) hypoplasia presenting the picture of a cardiac lesion, the mass of the cases belonging to this last group. Apelt[2] collected 100 cases from the literature and added an account of two cases, both of which were diagnosed during life. The subjects were young men aged seventeen and twenty-one years, of slight build and medium size, who had been capable of the usual amount of physical exertion, and had presented no symptom of disease. Both passed through a period of unusual physical strain just before the sudden onset of symptoms, which took place a few weeks before death. The picture was that of an acute dilatation of the heart with slight terminal cyanosis, œdema, ascites, the cardiac area enormously increased, and the pulmonary second sound markedly accentuated. The heart sounds were pure except toward the close in one patient, in whom a systolic mitral murmur developed. Postmortem, in both cases, the arteries were throughout thin, delicate, elastic, and of diminished calibre, and there was moderate hypertrophy with great pathological dilatation of the heart, although its valves and chordæ tendineæ were delicate, and healthy. Microscopic examination revealed an entire absence of fatty degeneration of the myocardium.

Van Ritoök analyzed 73 cases, 56 from the literature including the series of Burke and Apelt, and 17 from personal observation, and he enumerated the following points as of diagnostic value: (1) The youth of the patient. (2) Marked and obstinate anemia persisting in spite of all treatment. (3) The early development of fatigue in a young individual on slight physical exertion. (4) Subnormal temperature or only slight rise of temperature in febrile diseases. (5) Palpitation. (6) Hypertrophy of the left heart. (7) Acute cardiac insufficiency developing after comparatively slight physical strain. (8) Diminished resistance to infectious diseases.

ANOMALIES OF THE AORTIC ARCH.

Quite a wide variation of anomalous conditions of the aortic arch and its branches occur, the individual forms of which repeat themselves

[1] *Deut. Arch. f. klin. Med.*, 1901, No. 71, 187.
[2] *Deut. med. Woch.*, 1905, xxxi, 1186.

in different subjects with such similarity, that an underlying developmental error may be inferred. The units of the series may be summed up under the various headings of (1) double aortic arch, (2) right aortic arch, (3) origin of left subclavian artery, from (*a*) a patent ductus arteriosus, or (*b*) the pulmonary artery, (4) origin of the right subclavian artery from the descending thoracic aorta below the left subclavian artery, and (5) common brachiocephalic trunk. In all these the underlying defect is either a persistence of an embryonic arch which normally undergoes involution (double aortic arch, right aortic arch, left subclavian from patent ductus), or an arrested development of a portion of the embryonic arches that normally persists (right subclavian from thoracic aorta, common brachiocephalic trunk). In man the primitive aorta is at first double and of the six embryonic arches the first, second, and fifth disappear on both sides as well as the left sixth and the distal part of the left fourth, while the third parts persist as the carotid arteries, the fourth left as the aorta, the proximal portion of the right fourth, as the subclavian, and the left sixth becomes the pulmonary artery with the ductus arteriosus.

Double Aortic Arch.—In this anomaly, of which some 8 cases have been recorded, the aorta ascends to the right and turns backward and divides near the beginning of its transverse portion into two large trunks which lie parallel with each other and unite just beyond the insertion of the ductus to form the descending arch, enclosing between them an elliptical space in which the œsophagus and trachea lie embraced within the vascular circle thus produced. The posterior member of the pair, which is usually the larger, appearing as the true arch of the aorta, gives off the right carotid and subclavian, and lies behind the trachea. The smaller anterior limb lies below the other, appearing like a loop from it, and gives off the left carotid and subclavian, either as a simple trunk (left innominate) or as separate vessels. Examples are the cases recorded by Curnow[1] in a woman, aged eighty-seven years, and by Hamdi,[2] in a woman aged forty-five years. In the latter case the trachea and œsophagus were slightly compressed. Although no symptoms had been produced, the deformity of the trachea was sufficient to prove the possibility of a fatal obstruction.

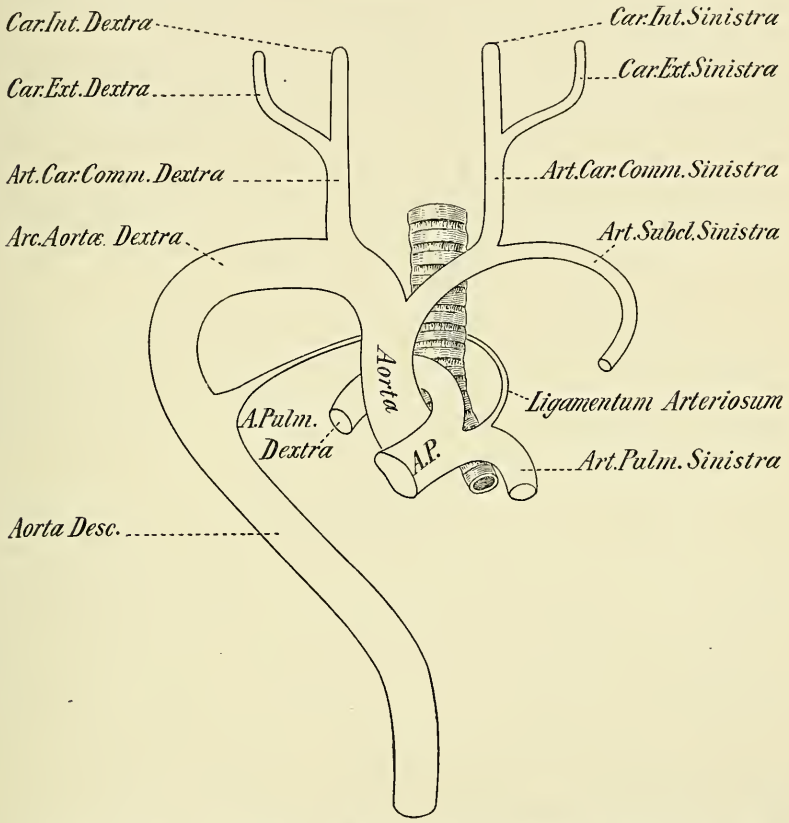
Henle explains the posterior limb of the double aorta as a persistence of the fourth right arch. The anterior limb represents the fourth left arch, and the two unite at the point of insertion of the ductus (sixth arch) to form the descending aorta as in the embryo, and as is persistent in the amphibia.

Right Aortic Arch.—In this anomaly the aorta is normal at its origin, but curves over the root of the left instead of the right lung, so that its *convexity* lies to the *left*, and it passes down on the right side of the aorta, the right recurrent laryngeal nerve hooking round the arch in the same manner as does the left under normal conditions. The left carotid, or, in some cases, a left innominate artery, arises from the front of the aorta shortly after its origin and represents the persistent *left*

[1] *Trans. Path. Soc.*, London, 1874, xxvi, 23.
[2] *Deut. med. Woch.*, 1906, xxxii, 1410.

aortic root. The right carotid rises next in about its normal situation, and then the right subclavian more posteriorly and to the right, while the left subclavian arises either (*a*) in its normal situation or (*b*) with the left carotid from the left innominate, or from a patent ductus or from the pulmonary artery.

Fig. 41



Dr. Kaufmann's case of right aortic arch with ligamentum arteriosum encircling the trachea and œsophagus. Diagrammatic representation following Evans' diagram of the survival of the aortic arches, to show that in the present case the fourth right arch (represented by the arch and trunk of the descending thoracic aorta), the left proximal part of the fourth left arch (represented by the left innominate and subclavian), and the left sixth arch (represented by the ligamentum arteriosum), survive, and that the trachea is necessarily encircled by the passing over of the ductus to the arch of the opposite side. The œsophagus is here omitted for the sake of clearness: *Car. Int. Sinistra*, left internal carotid; *Car. Ext. Sinistra*, left external carotid; *Art. Car. Comm. Sinistra*, left common carotid; *Car. Int. Dextra*, right internal carotid; *Car. Ext. Dextra*, right external carotid; *Art. Car. Comm. Dextra, right common carotid; Art. Subcl. Sinistra*, left subclavian; *Art. Subcl. Dextra*, right subclavian; *Arc. Aortic Dextra*, right aortic arch; *Art. Pulm. Sinistra and Dextra*, left and right pulmonary arteries; *D. A.*, funnel-shaped patent aortic end of ductus; *A. P.*, pulmonary artery. (Drawing by Prof. G. Adami, McGill University.)

The curve of the aorta passing from the right to left and then back to the right side of the vertebral column becomes very sinuous in those cases in which the ligamentum arteriosus or a patent ductus remains attached to the right aortic arch at its usual site of insertion opposite

or near the left subclavian. In these cases the ductus is forced to pass from its origin in the pulmonary artery, on the left side anteriorly, backward and to the right to meet the right arch which curves toward it *behind* the trachea and œsophagus which are thus again, as in double aortic arch, engaged in a complete vascular circle formed in this case by the aorta, ductus arteriosus (patent or obliterated), and the pulmonary artery. Four such cases are recorded, in two of which the ductus was obliterated; in the third, it was widely patent, and in the fourth case (a specimen in the McGill Museum presented by Dr. Kaufmann, which has been figured for me diagrammatically by Professor Adami, see Fig. 41), it was widely patent at its aortic end, but was closed beyond, the ligamentum arteriosum forming a long thick cord. In the latter case the aorta gave off a left innominate trunk and then curved backward soon after its origin and to the left, passing behind the trachea and œsophagus and gaining the right side of the vertebral column below. At the point where the convexity of the arch gains the left side of the trachea, it presents a deep triangular pouch, which represents the patent aortic end of the ductus, to the apex of which externally a cordlike structure of remarkable length and thickness, the ligamentum arteriosum, is attached. This ligament passed forward anteriorly to the trachea and œsophagus to its attachment in the left branch of the pulmonary artery, and encloses these viscera within the vascular circle formed by it with the aorta and pulmonary artery.

Such cases form a link between simple right aortic arch, in which the aorta lies entirely on the right side of the trachea, and double aortic arch in which trachea and œsophagus are completely embraced by a vascular ring. They throw light on the development of the latter, at first sight inexplicable, phenomenon. For, since a right aortic arch must pass behind the trachea to unite with the persistent sixth left arch which is represented by the ductus, it must do the same to unite with persistent left fourth arch which is represented by the anterior limb of the double pair. The whole situation is explained by the reflection that in the embryo these viscera occupy a position, not behind, but on the left posterior aspect of the primitive heart, and that the pairs of embryonic arches pass on either side of them to their destination in the dorsal aorta, so that if arches on opposite sides unite as they have done in the anomalies under consideration, trachea and œsophagus are bound to be encircled.

Left Subclavian from Ductus Arteriosus or Pulmonary Artery.—While the left subclavian is given off from the fourth right aortic arch, it is practically a continuation of the distal part of the sixth left arch represented by the ductus arteriosus to which its origin bears a constant relation.

Right Subclavian from Descending Thoracic Aorta.—In this anomaly the aortic arch has its normal course to the left, but the right subclavian is given off from a point in the thoracic aorta just below the insertion of the ductus arteriosus and passes up to its normal distribution. Here an arrest of the proximal part of the fourth right arch which normally forms the right subclavian has occurred, and the obliteration

of the distal portion which in the embryo unites the fourth arch with the aortic trunk has not taken place.

Common Brachiocephalic Trunk.—All four great vessels may arise by common origin, recalling the embryonic stage in which all the arches emerged together from the third carotid arch. A case is cited by Freyberger.[1]

Clinical Aspects.—The evidences presented during life and the clinical significance of all the above conditions are slight. In right aortic arch and common brachiocephalic trunk the aorta is apt to rise higher toward the neck than is normal, leading to violent pulsation in the episternal notch, which may lead to a mistaken diagnosis of aneurism. In the case of origin of the left subclavian from the pulmonary artery or patent ductus the left arm usually remains entirely free from cyanosis, which shows how far the system can accommodate itself under favorable conditions to an admixture of venous with arterial blood.

ANOMALIES OF THE CORONARY ARTERIES.

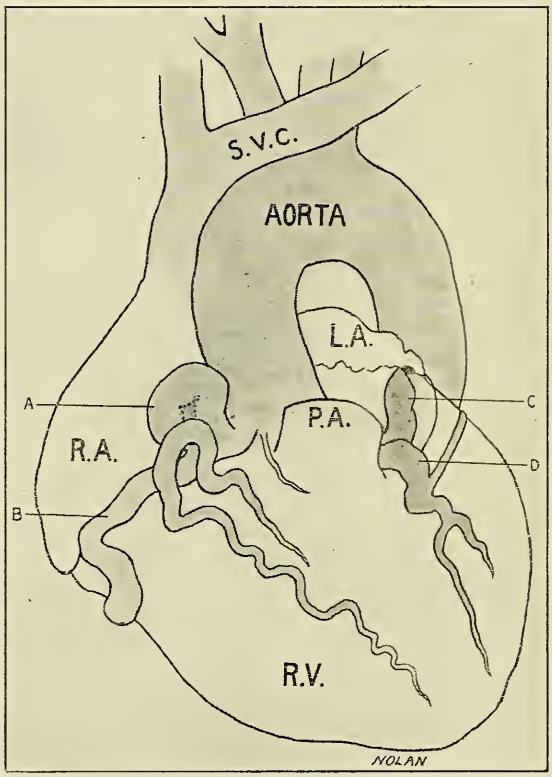
Anomalous Origin from the Pulmonary Artery.—A vessel may arise from a sinus of Valsalva of the pulmonary artery, and, meeting the branches from the aortic coronaries, produce a remarkable anastomosis of a cirsoid character. In Brook's first case, a vessel the size of a crow-quill sprang from the right anterior sinus of Valsalva of the pulmonary and passed down over the infundibulum of the right ventricle, there anastomosing with the aortic coronaries. In his second case a large anomalous artery arose from the same situation. It gave no branches to the heart but passed to the left and upward to enter a complicated mass of thin-walled arteries, which lay around the main pulmonary trunk and passed up along the trachea and behind the aortic arch. This mass received three other large vessels, one from the left subclavian, one from the right aortic coronary, and one from the posterior aspect of the transverse aortic arch. Krause's case is similar.

The McGill specimen (see Fig. 42), was from a woman aged sixty years, who died accidentally. The right coronary arose in its normal situation from the anterior sinus of Valsalva of the aorta by a much dilated orifice, and expanded directly after its origin into a huge thick-walled loop the size of a crab-apple, which projected upward some 2.5 cm. above the subepicardial fat, and gave off the descending branches from the loop. Both these and the main trunk of the vessel were wide, thick-walled, tortuous channels. No coronary arose behind the left posterior aortic cusp in the normal situation of the left coronary, but instead a large patulous opening lay in the floor of the dilated posterior sinus of Valsalva of the pulmonary artery. From this sprang a large thin-walled trunk of venous character, which divided about 1 cm. beyond its origin into two large branches, one of which ran to the left in the auriculoventricular groove in the course normally followed by the transverse circumflex branch of the left coronary artery, while the

[1] *Trans. Path. Soc.*, London, 1898, xliv, 44.
[2] *Jour. Anat. and Physiol.*, 1902–03, xxvii, 387.

other ran downward along the front of the interventricular septum in the position of its descending branch, and was here expanded into a large triangularly shaped venous sinus, 2 cm. in its widest diameter, and diminishing in size toward the apex. In the floor of this sinus were several thick-walled septa behind which large vessels opened into it from the myocardium.

FIG. 42



Aneurismal dilatation (arteriovenous ancurism) of branches of coronary arteries in a case of anomalous origin of the left coronary from the pulmonary artery. (From a specimen in the Medical Museum of McGill University, Montreal.)

The question of the circulation in the anastomosing vessels, in which blood from the systemic and pulmonary circulations must have mingled is of interest. Brooks suggests that the direction of the current must have been *toward* the cirsoid aneurism in the coronaries arising from the aorta, and toward the right ventricle in the coronary that arose from the pulmonary artery, which would thus drain the mass and would also send some arterial blood to the lungs.

In the McGill specimen the peculiar septa in the floor of the large venous sinus formed by the descending branch of the anomalous vessel, strongly suggested that the course of the blood was *toward* the pulmonary artery. This case is additionally interesting from the fact that the anomalous vessel was here clearly the left coronary, which was absent

from its normal situation and arose from the pulmonary. Both this and Brooks' second case were in elderly subjects, and the condition had not produced any manifestations during life.

Miscellaneous Anomalies.—Accessory coronaries may be present or both vessels may arise behind a single aortic cusp, or there may be a complete absence of one. A case has been recorded of an anomalous coronary sent to the lungs in pulmonary atresia.

ANOMALIES OF THE PULMONARY ARTERIES.

Accessory Pulmonary Artery.—A series of 10 cases has been collected from the literature by McCotter,[1] in which an anomalous artery had arisen from the aorta or its branches, and had supplied the lower lobe or the accessory lobe of one or other lung. In the case reported by himself, in a man aged sixty-five years, this artery was 7 mm. in diameter, and was given off from the front of the thoracic aorta on a level with the tenth dorsal vertebra, and passed up to the right between the folds of the ligamentum latum pulmonis to the lower margin of the right lung, where it ramified. The lung pleura and mediastinum were otherwise normal. In 8 of the cases collected the accessory branch was from the thoracic aorta, in one from the abdominal aorta, and in one from the seventh intercostal artery. In 5 cases the accessory branches supplied an accessory lobe and in 5 the lung was normal.

Pathogenesis.—The final explanation must be deferred until the origin of the pulmonary circulation is better understood. McCotter gives an interesting discussion. Accessory pulmonary arteries have been described in amphibia and reptiles, and are said to be normal in the latter. Thoma and Evans found that the blood vascular system in the embryo arises as a capillary plexus spreading in all directions. Such a capillary plexus forms caudally from the pulmonary arches and envelops the primitive lung *anlage* with a rich capillary plexus. In the case of the accessory pulmonary branch, this plexus must have formed laterally from a primitive thoracic aorta and joined the pulmonary plexus just as a capillary network extends to the limb-bud. The explanation of this anomaly is thus either (1) that this plexus always occurs but has failed to atrophy in the present case; or (2) that the plexus is only occasionally laid down, *i. e.*, is in itself an anomaly, and when present results in an accessory pulmonary branch. The condition has not shown itself to be of any clinical significance.

ANOMALIES OF THE SYSTEMIC VEINS ENTERING THE HEART AND OF THE PULMONARY VEINS.

Systemic Veins.—*Persistent left superior vena cava* is the commonest of these anomalies. It is not infrequent in conjunction with other cardiac defects, and occurred 26 times in our series. It is of little clinical

[1] *Anat. Rec.*, August, 1910, 291.

importance but is of great interest in cases where the congenital origin of the associated condition is questioned, as indicating the developmental nature of the latter. The cases may be divided into two groups: those in which the right superior cava is also present, and those in which it is absent, and the blood from the upper portion of the body enters the right auricle through the persistent left cava. A series of 4 cases of persistent left cava is published by Schutz.[1] In three of these the right cava was also present, in one it was equal in size to the left; in a second it was small and the left cava communicated with the left auricle by a valvular opening in its wall before entering the right auricle at the coronary sinus. In this case the apex of the heart was bifid, and the patient was a woman of thirty-eight of whom no other history was obtainable. In the third case the left superior cava was persistent but rudimentary. In Schutz's fourth case the *right superior cava was absent.* The left innominate veins emptied into the left innominate at the level of the left common carotid to form a left superior cava thicker than a man's thumb which widened into a bulbar swelling 4.5 cm. across, which entered the coronary sulcus and opened into the right auricle above the inferior vena cava. Habershon[2] reported a case of absence of the superior cava in a man aged thirty-seven years. The usual opening of the superior cava in the right auricle was marked by a smooth, white area of endocardium, like a closed foramen ovale, and there was extensive development of collateral circulation through the vena azygos major. The persistent left cava was formed by a union of the left jugular and subclavian and right innominate veins and emptied into the dilated coronary sinus. The recent literature on complete absence of the right superior cava with persistent left is given by Dietrich.[3]

A very interesting case is published by Beyerlein,[4] in a boy, aged one and a quarter years, of double superior vena cava, in which the orifice of the coronary sinus in the right auricle was obliterated by the overgrowth of an extensive network of Chiari. The persistent left cava received all the blood from the coronary veins and the heart, and emerged from the coronary sulcus at the normal situation, emptying into the right superior cava through the transverse branch. Two cases practically identical with this very rare anomaly are reported by Gruber[5] and LeCat (quoted by Gruber). Nabarro[6] describes a case of double superior cava in an infant of three months where the persistent left duct, smaller than the right, was joined by the left hepatic vein, which emptied with it into the coronary sinus. Here the left horn of the embryonic sinus venosus had evidently escaped obliteration.

A series of cases in which a *displacement to the left* of the superior cava has taken place so that its orifice comes to lie directly above the interauricular septum, and looks into both auricles, which has been

[1] *Virchows Arch.*, 1914, ccxvi, 35.
[2] *Trans. Path. Soc.*, Lond., 1876, xxvii, 79.
[3] *Virchows Arch.*, 1913, ccxii.
[4] *Frank. Zeit. f. Path.*, 1914, xv, 327.
[5] *Virchows Arch.*, 1885, xcix, 492.
[6] *Jour. Anat. and Path.*, 1902, xxxvii, 387.

described by Ingalls and others, and a similar condition of the inferior cava by Rokitansky, are described under auricular septal defects.

Pulmonary Veins.—An anomalous distribution of the pulmonary veins is much more common than is generally supposed, and quite serious deviations from the normal have been attended with surprisingly little results. Nevertheless, their displacement occurs in many complicated anomalies, and their repeated combination with these grave defects suggests a primary error in development in the pulmonary veins *anlage*. Quite a large series of cases of biloculate heart are reported in which the pulmonary veins were deflected from their entrance to the left auricle and were received by one or other of the great veins. Schroeder[1] gives a full discussion of the various anomalies of the pulmonary and systemic veins and traces their developmental origin, with especial reference to those cases, like his own, in which a complete defect of the interauricular septum was associated. Nabarro describes the pulmonary veins opening into the coronary sinus in an infant aged five and a half months, in whom all the blood from the systemic circulation must have passed through the patent foramen ovale.

In the cases reported by Ingalls,[2] Chiari and others, of defects at the upper part of the interauricular septum, the right pulmonary veins either entered the right auricle or the superior vena cava. In those reported by Borst and Stoeber[3] of an anomalous septum in the left auricle, the pulmonary veins entered the smaller upper chamber in the left auricle to the right of the anomalous septum, which evidently represented the septum primum, deflected to the left by the entrance of the pulmonary veins too far to the right side. In all, the primary defect is apparently the deflection of the pulmonary veins.

Ramsbotham describes a case in which the left pulmonary entered the left subclavian, and the right pulmonary the portal vein, and in three others (Arnold, Bochdalek, Geipel) the right and left pulmonaries entered the portal vein together as a common trunk. The pulmonary veins of both sides may enter the left auricle as a single or as two trunks. Here the original single vein has not been taken up in the wall of the auricle as occurs in normal development.

The *clinical significance* of these conditions depends less upon the defect itself than upon the associated developmental conditions.

DIAGNOSIS, PROGNOSIS, AND TREATMENT OF CONGENITAL CARDIAC DISEASES.

Differential Diagnosis.—In the diagnosis of congenital cardiac disease two questions are to be considered: a congenital is to be distinguished from an acquired lesion, and the differentiation may be attempted of the particular defect. The first of these is the more important as well as the simpler problem. It is necessary both for a wise prognosis and for proper treatment to recognize the congenital nature of the lesion,

[1] *Arch. für. Virchow's path. med.* ~~Klin. Med.~~, 1911, ccv, 122.
[2] *Johns Hopkins Hosp. Bull.*, 1907, xviii, 136.
[3] *Virchows Arch.*, 1908, exciii, 252.

and this can usually readily be done. The following conditions are significant of the presence of a defect: (*a*) The youth of the patient. (*b*) A history of symptoms originating in early childhood or in infancy, and of the absence of any event, as rheumatism or endocarditis, which could have led to an acquired lesion. (*c*) The cyanosis when this is present, and the symptom complex associated with it. (*d*) The presence of atypical physical signs.

The diagnosis of the various defects from each other is a more difficult task. In some of the most complicated forms of congenital cardiac disease both signs and symptoms may be conspicuous by their absence. And on the other hand, several anomalies are frequently combined in the same case, so that a bizarre picture is liable to be produced, even in the presence of marked physical signs. Nevertheless, a careful study of the literature, and the application of this at the bedside has convinced the writer that in the great majority of cases auricular and ventricular septal defects, abnormal communication between the aorta and pulmonary artery, patent ductus arteriosus, subaortic stenosis, and coarctation of the aorta, all of which conditions are characterized usually by *slight* or *absent cyanosis*, can be distinguished from each other and from pulmonary stenosis or atresia, and from those forms of biloculate and triloculate heart, persistent truncus arteriosus and transposition of the arterial trunks, *in which the cyanosis is a more conspicuous feature.* This statement has the authority of Hochsinger, whose special work along the line of congenital defects convinced him that the differentiation of cardiac defects is largely a question of familiarity with the clinical features.

Cyanosis is the rule (to which a few exceptions occur) in pulmonary stenosis and atresia, in complete defects of the septa, as biloculate or triloculate heart or persistent truncus arteriosus, and in transposition of the arterial trunks. It is frequently absent, but may be present and this especially as a terminal event, in patent foramen ovale and in defects of the interauricular and interventricular septa. Cyanosis is usually *absent*, except during dyspnœic attacks, in patent ductus and in coarctation and hypoplasia of the aorta.

Dyspnœa, though always present to a certain degree when cyanosis is advanced, does not appear to bear a definite relation to the degree of deficient aëration but evidently depends on some other factor as well. It is thus characteristic of many cases, such as patent ductus, patent foramen ovale, or septal defects, in which no trace of cyanosis is seen, shortness of breath and palpitation on exertion from early childhood, being quite frequently complained of. The same is true of *dyspnœic suffocative attacks* with transient cyanosis which form an important diagnostic feature of such cases.

The distinctive character of the *physical signs* in those defects which are of clinical significance have been discussed under the individual lesions but may be briefly summarized. A harsh, *systolic murmur* and thrill localized over the upper part of the precordium and of diminished intensity or inaudible at the apex is characteristic of pulmonary stenosis and of septal defects. It may in a few cases be heard best at the apex,

and it may vary in rhythm, particularly in septal defects. Both in pulmonary stenosis and in patency of the duct the murmur usually has its maximum intensity high up over the second left interspace and may be heard beneath the left clavicle. That of the auricular and ventricular septal defects is heard over the third and fourth left interspaces. Murmurs of congenital lesions, when heard in the back, are usually due to patency of the duct or to septal defects. A precordial *thrill* with the same localization as the murmur is present in about 15 per cent. of congenital defects with physical signs, its presence as a rule corresponding to the degree of harshness of the accompanying murmurs.

In *defects* of the *interauricular septum* the murmur is often post-diastolic or presystolic, and in patent foramen ovale presystolic and systolic murmurs may combine or alternate with each other, and may vary with change of position, their inconstancy supplying a differential point.

In *patent ductus*, a harsh rumbling machinery murmur, beginning toward the close of systole and continuous throughout the cardiac cycle is present in a certain number of cases, and when it occurs is pathognomonic; in others the murmur is systolic or (rarely) diastolic. The pulmonary second sound is here usually accentuated and helps to differentiate patent ductus from pulmonary stenosis, in which the pulmonary second is usually (not always) weak or absent. An abnormal area of dulness above and distinct from the cardiac dulness, in the first and second left interspaces (Gerhardt's sign), is also significant of the latter stages of patent ductus, as indicating a dilated pulmonary artery. This sign may be produced also by retraction of an atelectatic left lung (Hochhaus), so is not positive unless confirmed by the *x*-rays.

A powerful *diastolic* murmur and thrill with maximum intensity over the second and third interspaces, and an accentuated second pulmonary sound characterized several of the cases of abnormal communication between the lower part of the aorta and pulmonary artery (defect of the aortic septum) recorded.

Complete *transposition* of the arterial trunks has been diagnosed by the absence of physical signs in the presence of marked cyanosis, and an accentuated pulmonary second sound (Hochsinger).

Coarctation of the aorta is to be recognized by the evidences of the collateral circulation when this has been established, hypertrophy of the left heart, the frequent association of an acquired aortic insufficiency, and a reduction in the force of pulsations in the lower extremities as compared with the upper.

The above are a few of the indications by which typical cases may be distinguished from each other. But in this subject it should be remembered that hard and fast lines may not be drawn. Thus rhythm, maximum intensity, transmission of murmur or thrill, and all other manifestations of the defect will be found to vary with the associated cardiac conditions, valvular and myocardial, congenital and acquired, far more here, where so wide a range of combinations is possible, than in the acquired forms of heart disease. For this reason we look with interest to the introduction of the newer methods of precision in this difficult

and little studied field. Several positive findings have already been recognized and are indicated below. There is good reason to believe that their further application will supply us with a more exact knowledge upon the differential diagnosis of congenital defects.

Graphic Methods.—*X-ray Examination and Orthodiagraphic Tracings.*—Definite information upon the existence of hypertrophy of the ventricles and dilatation of the auricles is to be obtained from the skiagraph. Examination of the shadow at the base of the heart shows also a distinct widening in the presence of dilatation of one or other of the great trunks. When the pulmonary artery is the one dilated the widening appears as a distinct bulging on the left side just above the upper border of the heart, forming an "*x*-ray cap" in the position of the so-called Gerhardt's dulness. Dilatation of the aorta is indicated by an increased shadow to the right of the median line in the same situation. Conversely, hypoplasia of the pulmonary artery is indicated by a narrowing of the shadow to the left of the heart's base. These points and the typical shape which the ventricular portion of the heart assumes in the various valvular lesions are well shown in the heart-silhouette obtained by the orthodiagraphic tracing. Groedel[1] has figured the outline obtained both in the various acquired valvular lesions and also in congenital pulmonary stenosis, patent ductus arteriosus, and coarctation of the aorta and points out that in patent foramen ovale and in ventricular septal defects there is no change observed at the site of the great vessels so that unless hypertrophy of the ventricles has occurred the silhouette is normal.

Fluoroscopic Findings.—Deneke[2] diagnosed a case of interventricular septal defect in transposition of the arterial trunks by the appearance on fluoroscopic examination. The heart showed a moderate degree of hypertrophy of the right ventricle, and this chamber formed the right border of the heart in place of the right auricle as normally occurs, so that the strong pumping movement of the ventricle could be seen on the *right* border as well as on the left, instead of the fluttering auricular movement normally seen in this situation. Deneke describes the appearances as follows: "In normal hearts the movement of the right border is seen on the fluoroscope as a sharp auricular twitching preceding the contraction of the left. Its character can be readily distinguished as auricular, *i. e.*, a short fluttering contraction followed by long, passive dilatation. The movement on the left border is slow, lasting much longer than that of the auricular, and is a strong pumping motion followed by a short delay in the contracted state, then a gradual dilatation which is slower than the ventricular contraction, but much quicker than the dilatation of the auricles."

The Electrocardiographic Curve in congenital hearts has been studied by Lewis,[3] Owen,[4] Nicolai,[5] Ratner,[6] Groedel and Mönckeberg,[7] and

[1] *Deut. Arch. f. klin. Med.*, 1911, ciii.
[2] *Ibid.*, 1906, lxxix, 38.
[3] *Clinical Electrocardiography*, 1913.
[4] *Heart*, iii, 113.
[5] *Berlin, klin. Wchnsch.*, 1911, xlviii, 51.
[6] *Berlin Thesis*, 1912.
[7] *Cent. f. Herz. u. Gef. Leid.*, January 1, 1913.

others. So far only a few positive points have been elicited, but these are sufficient to indicate the value of the cardiogram in this connection. (1) A "*negative initial Schwankung*" representing a deep exaggeration *of the S wave, in lead I*, has been observed in many congenital cases, and was described by Nicolai and Steriopulo as pathognomonic of cardiac defects. It is merely significant, however, of the extreme right-sided hypertrophy so common in these cases in which both right auricle and ventricle are involved, and is seen also in acquired mitral stenosis where the same condition of marked right-sided hypertrophy and dilatation occurs; as a corroborative sign it is often of use. (2) *An extreme amplitude of curves in several leads* was observed by Lewis in congenital cyanosis and is described by him as a "valuable sign of congenital valve or septal defects." (3) Finally, the electrocardiogram in true (mirror-picture) dextrocardia when the heart is transposed upon itself, supplies the most positive sign of this abnormality that we possess. In this case Lead I is completely reversed upon itself, and Lead II takes the place of Lead III, exactly the same tracing being obtained as when the leads themselves are reversed in a normal individual. The transposed electrocardiogram decides clearly between this condition and a simple dextroversio cordis. For a comparison of the electrocardiograms in these two conditions (see Fig. 22).

The polygraphic tracing may show a positive venous pulse of mitral insufficiency with communication between the two sides of the heart. In the absence of mitral stenosis (in which auricular fibrillation is so common and may give rise to this condition) and when other signs of tricuspid insufficiency are lacking this point may be of diagnostic value.

Estimation of the Oxygen Content of the Alveolar Air.—An important diagnostic point between those defects due to abnormal communications between the right and left sides of the heart, and those due to pulmonary obstruction has been supplied by Plesch,[1] working in Kraus' laboratory. In septal defects and patent ductus, there is usually an admixture of arterial blood with the venous current entering the lungs through the pulmonary artery, owing to the fact that under normal conditions the pressure in the aorta is greater, so that blood passes from left to right through the defects. Plesch estimated the amount of oxygen in the alveolar air expired from the lungs which he obtained by his method (described by Boothby and Peabody[2]), and found that in these conditions the venous blood passing to the lungs is reduced; that is to say, in terms of percentage of its oxygen content, the latter (O_2) is raised. This was also demonstrated in two cases of Vaquez disease (polycythemia with splenomegaly) in which the oxygen content of the alveolar air was examined by Senator-Lowy and v. Bergmann. On the other hand the alveolar air in cases of acquired valvular diseases and in one of congenital pulmonary stenosis was examined and showed no deviation from the normal. These figures and those showing the

[1] *Berlin. klin. Wchnschr.*, 1909, xlvi, 392.
[2] *Arch. Int. Med.*, 1914, xiii, 502.

amount of oxygen consumed are shown in the table taken from an article by Kraus.[1]

	Normal.	Polycythemia.			Congenital defects.			Mitral insufficiency.	Mitral stenosis.	Aortic insufficiency.
		Senator's case.	v. Bergmann's cases.		Persistent ductus arteriosus.	Septal defect.	Pulmonary stenosis.			
			I.	II.						
O_2 used pro kilo and minute.	3.52	4.18	4.02	4.38	4.83 4.40	5.03	6.74	3.86	4.62	4.11
Reduction of venous blood in percentage of O_2 content.	64	83	81	64	83 87	86	66	64	64	62

The differential diagnosis between the cyanosis and clubbing of congenital cardiac diseases and other forms is discussed under cyanosis.

Prognosis.—The duration of life has been considered in detail in connection with those defects that are of clinical interest, but a few generalizations may be made. The prognosis varies with the lesion and includes a wide range of possibilities, but is in general grave; this is based upon the direct interference with the circulation by the defect itself, and upon the well-known tendency of certain anomalies to become the seat of a future malignant endocarditis.

Among the least harmful forms of congenital cardiac disease may be mentioned anomalous septa in the auricles, patent ductus arteriosus, and coarctation of the aorta with extensive collateral circulation, which may exist until past middle life without symptoms, frequently terminating then with a general failure of compensation under some undue strain. Localized defects of the interauricular and interventricular septa belong likewise to the more innocent lesions which may give rise to symptoms, or may be present indefinitely without producing any effect upon the circulation, becoming serious only upon the advent of some pulmonary complication raising the pressure in the right heart, or through the engrafting of a malignant endocarditis along the edges of the defects.

In the more complicated defects life is correspondingly shorter. Young's patient with cor biatriarum triloculare and anomalous septum attained the age of thirty-nine years, and Holmes' twenty-four years, but these are rare exceptions, the subjects of biloculate and triloculate heart usually dying in infancy. This is true also of persistent truncus arteriosus, although a patient reaching twelve years is recorded by Crisp. In pulmonary stenosis early adult life is not uncommonly attained, but is rarely passed, the patients dying as often of tuberculosis as of the direct effects of the lesion. Here again in exceptional cases life may be prolonged, Vulpian recording pulmonary stenosis, *rechtslage* of the

[1] Chart from Kraus' article, *Berl. klin. Wchnschr.*, 1910, lxxiv, 230.

aorta, and defect of the septum in a man who died at the age of fifty-two years. The average duration of life in pulmonary stenosis is fifteen years, and in atresia 2.25 years in our series.

As graver conditions proving almost inevitably fatal during the first weeks or months of life may be enumerated: complete transposition of the arterial trunks without defect of the interventricular septum, pulmonary atresia with closed interventricular septum, tricuspid atresia, and aortic atresia, which is, indeed, the most serious of all, nearly all the cases recorded dying in the first two weeks of life, and many within a few hours of birth. The same is true of most forms of ectopia cordis. Finally, it is to be remembered that of the more complicated anomalies many must perish in the early stages of embryonic development, as only those in whom compensatory conditions arise survive until birth.

The prognosis depends largely upon the effects of the lesion upon the circulation, that is, upon the amount of deficient aëration produced, and upon the compensatory powers. For this reason symptoms will frequently prove a better guide to the immediate future than physical signs. Such conditions as septal defect, for instance, may give marked murmurs and thrill, yet lead to no hampering of the heart's action and to little interference with oxygenation until some additional factor, such as obstruction in the pulmonary circulation supervenes. Persistent cyanosis, a continued low temperature, a marked increase in the number of red blood cells (above 5,500,000), and dilatation of the heart, all point to a grave disturbance of the circulation and to a rapidly fatal issue. On the other hand, the entire absence of cyanosis and its attendant phenomena does not always argue a favorable prognosis, for in such cases sudden death may occur without any warning, either quietly, or in a paroxysm of cyanosis with dyspnœa. The embarrassment to the circulation which the lesion itself entails is not the only source of danger. Grave danger lies also in the frequent intercurrence of a malignant endocarditis, and in the fact that infections or bronchopneumonia are apt to prove rapidly fatal. The liability of patients with pulmonary stenosis to tuberculosis, and the frequent termination by sudden cerebral complications, are other unfavorable factors. These considerations indicate the extreme gravity of the more pronounced cases, and the fact that even in the more innocent forms of congenital cardiac disease the prognosis must be framed with reserve and caution. Among the better class, where good hygiene prevails and the most suitable conditions of living can be sought, the outlook is of course better than among the children of the very poor.

Treatment.—This may be said to begin with the care of the mother during her pregnancy, for a study of the etiology clearly shows that to some unhealthy condition in the environment of the embryo or in the parental organism, rather than to an ancestral tendency toward anomalous growth, the majority of cardiac anomalies owe their origin.

The treatment of a patient suffering from congenital cardiac disease must be largely symptomatic or palliative, or directed to the preventing of complications. The indications here are to do all that is possible to facilitate the oxygenation of the blood, to avoid additional taxation of

the burdened circulation, and to shield the patient from accidents or illnesses which increase the pulmonary or systemic obstruction, remembering always that in the majority cyanosis first develops on the addition of some such factor to the pathological conditions produced by the lesion itself. A carefully regulated life, a plentiful supply of light, fresh air, and warmth, the maintenance of an equable bodily temperature, the avoidance of mental agitation and of undue physical exertion, rest, and quiet forms of exercise, where this last is permitted by the condition of the patient, are all essential. The diet should be carefully ordered, light and nutritious, and the often capricious appetite watched. Free action of the excretory organs, especially of the skin, should be promoted and the child kept clothed with flannel. Sudden changes in the external temperature must be avoided and, when possible, resort should be had to a warmer winter climate. Exposure to cold or wet, or to any of the causes of rheumatism, should be avoided on account of the great liability to acute endocarditis. When adult life is attained, choice of light employment which does not call for sudden or great physical exertion is important. In women child-bearing is fraught with danger.

Operative interference in patent ductus arteriosus in the form of ligation of the duct, was suggested by Munro[1] on the ground that a probable diagnosis is now possible and that the vessel lies in an accessible situation. The fact that distinctive signs occur only after pulmonary dilatation has taken place and a certain adjustment of the vessels to the new order of the circulation has set in, would make one hesitate to resort to so radical a measure, which might introduce a new factor of disturbance.

When cyanosis has developed, the administration of oxygen has been suggested as likely to be useful in relieving dyspnœa. Gibson and others report a negative result from its use in several cases. For the relief of the dyspnœic attacks diffusible stimulants are of benefit and should be kept at hand; and in infants the hot mustard bath is useful. The frequent syncope may best be relieved by strychnine. When failing compensation sets in, the usual treatment of rest and cardiac tonics is to be employed, and here strychnine is said to give better results than digitalis.

Thus, in a very few words, a careful hygiene and an expectant and preventive treatment may be summed up as the only available assistance that can be given. The condition does not admit of cure, but permits of amelioration and of arrest of the downward trend of the disease.

[1] *Ann. Surg.*, 1907, xlvi, 335.

CHAPTER XI.

DISEASES OF THE ARTERIES.

By Sir WILLIAM OSLER, Bart., M.D., F.R.S.

ACUTE ARTERITIS.

Mistaking staining of the intima for inflammation, the older writers described arteritis as a common event in many diseases. In the early years of the nineteenth century Cruveilhier and others believed that it was the cause of the clotting of the blood in the vessels, and that it arose spontaneously as a complication in the fevers. Virchow took an opposite view, viz., that the thrombosis was the primary event, and the arteritis always secondary, whether the clot was embolic in origin or formed at the site from conditions of the circulation or the blood. Of late years we have learned to recognize that the arteritis is sometimes a sequel of the clotting, sometimes due to primary changes in the vessel wall.

Secondary Arteritis.—Secondary arteritis occurs when a local infection attacks the vessel wall from without, as in abscess formation, etc.; or when the intima is injured and inflamed as a result of an infected embolus or an infected marantic thrombus. This form will be considered in connection with embolism and thrombosis, in the course of which it is an incident.

Primary Arteritis.—Primary arteritis is a rare disease, met with as a complication in the acute infections, and occasionally as an independent malady. In ordinary medical work it is most frequently seen in typhoid fever, but its rarity may be judged of from the fact that in this disease there were only 5 instances in 1500 cases at the Johns Hopkins Hospital.[1] In smallpox, scarlet fever, influenza, and pneumonia, cases have been observed. It is less common in rheumatic fever, diphtheria, yellow fever, typhus, and measles. In typhoid fever, pneumonia, and diphtheria the organisms of the disease have been found in the vessel wall. In direct infection from the blood the intima is first involved, and there may be small vegetative out-growths such as we see on the intima of the valves, but this is rare. In other cases the infection is conveyed through the vasa vasorum, and the adventitia and media are first involved. The grades of alteration in the vessel depend upon the type and virulence of the organism. The intima alone may be affected, with the result of the formation of a thrombus; in other cases the vessel wall is acutely inflamed and there are swelling and infiltration of the neighboring tissues.

[1] Details of these are given in Thayer's Jerome Cochran Lecture, *Johns Hopkins Hospital Bulletin*, 1904, xv, 323.

Symptoms.—The symptoms depend upon the vessels affected. In the external arteries, as in the femorals or popliteals, there is pain, often of great severity in the course of the vessel, spontaneous or on movement, and an increase in the fever with swelling over the vessel and sometimes redness. The pulse below is obliterated; the limb is at first pale and cold, and then gradually becomes livid at the periphery. When the femoral is obliterated, whether or not gangrene follows will depend upon the rapidity with which the vessel is blocked, and the extent of the thrombus. There are cases which look threatening at first, and in a few days the signs of obstruction pass away. In other instances the process extends and both legs may become affected.

Gangrene is only too apt to follow obstruction of the femoral artery in the acute infections. It is not always easy to determine whether the thrombosis results from a primary arteritis or an embolus. Suddenness of onset and the existence of conditions favorable to embolism point to the latter. There are cases in which the onset is severe, and for a few days the symptoms suggest that gangrene will follow, and then the circulation is reëstablished and color returns to the limb. Parietal thrombosis with only partial occlusion of the vessel may be present. Of our 2 cases of typhoid fever in which the femorals were affected, gangrene followed in one, in the other the condition cleared in a few days. In 1 case the brachial was involved at the bend of the elbow.

Arteritis of the internal vessels is still more rare. Of 2 of our cases in which the cerebral vessels were affected in typhoid fever, in 1 on the ninth day of the disease, in the other on the nineteenth, both proved fatal. In the arteries of the kidney, the spleen, and occasionally of the heart, a spontaneous clotting may occur as a result of inflammation in the acute infections.

Primary Multiple Arteritis.—There are instances in which in the course of a few days, without the existence of any local disease, a thrombo-arteritis occurs in many vessels, associated with high fever and signs of an acute infection. The writer has reported a remarkable case in a man, aged twenty years, who had had typhoid fever two years previously. He was admitted to the Philadelphia Hospital with fever, rapid pulse, diarrhœa, and abdominal pain. He had thrombosis of both femorals and iliac arteries and of the lower two inches of the abdominal aorta, and of two large branches of the splenic artery. There were infarcts in the spleen and in the kidney.

Acute Aortitis.—Lesions of the aorta due to acute inflammation are exceedingly rare. The term aortitis has been used very loosely to describe conditions which are degenerative rather than inflammatory, and which come under the general category of arteriosclerosis. It is an altogether false conception of the process to speak of the degenerative plaques of the intima and the foci of medical necrosis met with so commonly in the infections as acute aortitis. The process occurs under the following conditions:

1. **Acute Vegetative Aortitis.**—In pneumonia, in rheumatic fever, and in the acute septic infections, the lining membrane of the arch may present numerous irregular vegetations identical with those on the valves.

The condition is rarely if ever met with apart from aortic or mitral valvulitis. It is exceedingly rare, and the writer has not seen more than three or four instances. The outgrowths may be firm and warty in character, or a perfectly smooth intima may present a series of globose vegetations. Acute aneurism may be associated with the process. There may be half a dozen small sacs. Cases have been reported, particularly in France, in connection with rheumatic fever. Pneumococci and staphylococci have been found in the vegetations.

2. **Acute Mesaortitis.**—This is much more common, particularly in syphilis. Within a few weeks a localized productive aortitis occurs, largely confined to the media, but quickly involving the other coats, and leading to aneurism or to an acute dilatation of the part of the vessel affected, or to rupture with a dissecting aneurism. This is a type of aortic disease to which the term "acute aortitis" may very properly be applied, and will be dealt with under the subject of aneurism. Other varieties of acute infective mesaortitis are conveyed through the vasa vasorum and there are foci of softening, sometimes of acute suppuration, in the middle and outer walls of the artery. This may lead to localized weakening, so that the intima over the spot is split. As many as four, five, or six of these small fissures may be seen on the intima of the arch, each one leading into a little focus of softening and dilatation. Sometimes the edges of the splits are covered with luxuriant vegetations. Acute aneurism is apt to follow, which may rapidly prove fatal. To this condition, occurring in the course of an infection like rheumatic fever, the term "acute aortitis" is really applicable. There are instances in which in an aorta with perfectly smooth intima there is a small erosion like an acute ulcer, leading directly into an aneurism. The writer has reported a remarkable case, with the illustrations, in which in the lower part of a normal looking descending aorta there was a linear perforation 1.5 cm. in extent, which led directly into a small aneurismal sac which had ruptured into the œsophagus. The woman was only thirty-five. There was no endocarditis. The probability is that she had an acute mesaortitis comparable with that which may be produced in animals experimentally, and that over this small spot the intima fractured.

Symptoms.—The *symptoms* of acute aortitis are exceedingly vague. It is one of the most interesting points in comparative medical literature to read the extended description of the disease as given by French writers, and then to note the silence of American, English, and German authors on the subject. Except in syphilis, the writer has never made the diagnosis of acute aortitis; here the pain, often anginal in character, and the development, under observation, of aortic insufficiency, give decided indications of disease at the root of the aorta. In a case of rheumatic fever, or acute sepsis, signs indicating acute dilatation of the arch of the aorta would be suggestive. It must be borne in mind, however, that a large majority of cases of so-called aneurism occurring in children in connection with rheumatic fever, are instances of dynamic dilatation of the aortic arch in connection with aortic insufficiency. An abdominal aortitis is recognized by French writers, characterized by pain, throbbing, increased mobility, and a loud systolic murmur, with a relatively higher

blood pressure in the femorals than normal. Clinically, the condition is quite as vague as the acute thoracic aortitis.

A special form, *tuberculous aortitis,* may be mentioned, of which a few cases have been described. In Flexner's case there was a small tuberculous nodule just below the left subclavian artery, seated directly on the intima, which everywhere else was smooth. Tubercle bacilli and giant cells were present and there were tubercles in other organs.

3. **Acute Periaortitis.**—Occasionally in suppuration in the neighborhood of the aorta, as in connection with a lymph gland in the anterior mediastinum or in suppurative processes in the abdomen, the adventitia of the aorta may be involved, and present a focus of suppurative softening.

CHRONIC ARTERITIS. ARTERIOSCLEROSIS

Definition.—A general disease of the arteries, characterized in the small vessels by thickening of all the coats, and in the larger by gelatinous swelling, necrosis, fatty degeneration and calcification, the processes to which the name *atheroma* has been given.

Sometimes the term arteriosclerosis is limited to the smaller vessels, and that of atheroma to the larger arteries. On account of the irregularities due to calcification and atheromatous erosions, the name of *endarteritis deformans* is given to the process in the larger arteries.

Etiology.—There are four great factors in the causation of arteriosclerosis—the normal wear and tear of life, the acute infections, the intoxications, and those combinations of circumstances which keep the blood tension high.

1. **Wear and Tear of Life.**—Among organs the bloodvessels alone enjoy no rest. Not only does a ceaseless rush of fluid pass through them at a speed of 10 inches a second, but the walls of the main pipe are subjected to a distending force of 25 pounds to the square inch, 60 to 80 times a minute, 80,000 to 100,000 times in the twenty-four hours. The heart has rest in diastole, but distended by the charge from the left ventricle, the arteries pass it on partly by the natural elasticity of the walls, partly by an active contraction of the muscle fibres. Like other organs they live under three great laws—use maintains and in a measure sustains structure; overuse leads to degeneration; in time they grow old, in threescore or in fourscore years the limit of their endurance is reached and they wear out.

The stability of tubing of any sort depends on the structure and on the sort of material used; and so it is with the human tubing. With a poor variety of elastic and muscular fibres in the bloodvessels, some are unable to resist the wear and tear of everyday life, and have at forty years of age arteries as old as those of others at sixty. One day, at a meeting of the American Medical Association, Dr. Henry Martin (of vaccine fame), who possessed all histrionic gifts, was demonstrating samples of Esmarch's bandages, one of which, as he spoke, he broke into fragments with great ease, while another resisted all his efforts. "They look the same," he said, "and they are made of the same substance, but they are not the same, one is shoddy, the other is the genuine article." And so

it is with our arteries. They look the same macroscopically and microscopically, but they differ in different individuals in the quality of the materials used and the capacity to resist the ordinary stress of life. Not only are there individuals, but whole families, with "shoddy" bloodvessels. Hence the truth of the old saying attributed to Cazalis, "a man is as old as his arteries." In the building of the human body, as of chaises, there is, as the Autocrat says, "always somewhere a weakest spot," and too frequently this is in the circulatory system.

The conditions of modern life favor arteriosclerosis, as a man is apt to work his body machine at high pressure, and often takes less care of it than of his motor. The best express engine from the Baldwin works run day by day at maximum speed will not last one-tenth of the time it would do if it were not so pushed. But nowadays, with the human engine it is top-speed or nothing, and we cannot wonder that it early shows signs of hard usage. In the fourth or fifth decade, even with the best of habits in eating and drinking, the incessant strain and anxiety of public life or of business may lead to degeneration of the bloodvessels. The recent statistical proof that the average age of death in American men has diminished testifies to this. Mental exertion is not of itself injurious, and the life of the student need not be one of great tension, but the mental exertion of the modern business man is of a different kind. Competition is so keen and the environment so stimulating that, even without social or political ambitions, high pressure seems a necessity. The tragedies of life are largely arterial. Represented in the old mythology as winged, Nemesis, the goddess of the Inevitable, may still be pictured with a wheel, the wheel of life, to the ceaseless revolutions of which the circulation ministers. How often does her fatal touch call away in their prime the best and the bravest—men whose only fault has been the unselfish abuse of the body machine!

After forty it is exceptional to examine the arteries without finding evidence of degeneration—here and there a small plaque of atheroma, an occasional streak of intimal fatty degeneration, and with this the mitral and aortic cusps may have lost just a little of their delicate tenuity. With advancing age the arteries become thicker and the atheromatous changes more marked. As a rule, in the very aged not only the smaller arteries are thickened, but the aorta and its main branches show extensive changes with calcification. Occasionally, however, a very old person may have singularly healthy bloodvessels. It is not the case, as so often quoted, that Harvey found the vessels of Parr, who lived to be one hundred and fifty-two (?), to be healthy. He does not mention them. Living quieter lives and with less stress and strain, women are not so frequently the subjects of arterial changes, and in consequence they last longer. In infants and young children arteriosclerosis occurs: (1) As occasional patches or flakes, or even calcified foci, in the vessels of the newborn. (2) In infants dying of the acute infections, streaks of fatty degeneration of the intima and foci of necrosis of the media are not uncommon. (3) Widespread arteriosclerosis of the smaller vessels may occur without nephritis and without recognizable cause. Two or three cases may occur in the same family. (4) In congenital syphilis, diffuse or localized

sclerosis of the arteries may occur, sometimes early, sometimes as a late manifestation in *syphilis hereditaria tarda*. Fremont-Smith,[1] who reviewed the literature of arteriosclerosis in the young, found no difficulty in collecting 144 cases.

2. **The Acute Infections.**—Of the acute infections, *syphilis* is the one with a special predilection for the arteries. There are changes best described as acute productive arteritis, and there are degenerative changes which come in the category of chronic arteritis. The special features of syphilitic aortitis will be described later. The lesion may be a chronic obliterative endarteritis, limited to a special group of vessels, as in the brain, the heart, or the vessels of the extremities. Extensive arteriosclerosis in infants and in children is very often syphilitic, and in the acquired disease a slow, progressive arteriosclerosis may exist in combination with other parasyphilitic manifestations. We have learned to recognize the great frequency in scarlet fever, measles, diphtheria, smallpox, and influenza, of foci of arterial degeneration. It has long been known that in typhoid fever areas of necrosis and fatty degeneration are met with in the aorta. The observations of Thayer show how important are the cardiovascular relations of this disease. Of 52 postmortems at the Johns Hopkins Hospital, in which notes of the condition of the aorta were made, evidence of sclerosis were present in 30, and in 21 of these the changes looked recent. It is remarkable that out of 62 instances in which the condition of the coronary arteries was stated, in 19 sclerotic changes were present, and in 13 of these the changes were recent. One of our house physicians, a very vigorous man of twenty-five, died at the end of the third week of typhoid fever. There were patches of endarteritis at the root of the aorta and numerous patches of yellowish sclerosis in both coronary branches. Thayer examined 189 patients who had had typhoid fever in the hospital within fourteen years, and 40 per cent. of the persons between the ages of ten and fifty presented palpable radial arteries compared with 17.5 per cent. of a series of control cases. The change may be in connection with the higher blood pressure which he found to prevail in these patients.

At the Franz-Joseph Hospital, Vienna, Wissal examined 300 bodies of children dead of acute infections, and in 80 found signs of arteriosclerosis, usually in the form of ordinary patches in the aorta and larger branches, but the small vessels were also found involved. It is interesting to note that he found the chief changes, which were in the media, to bear a striking resemblance to those produced in experimental aortitis in animals.

Tuberculosis is another disease with which arteriosclerosis is frequently associated. It has been observed by many writers that in chronic pulmonary tuberculosis the superficial bloodvessels are apt to be thickened. It is rare to examine a patient with tuberculosis of the lungs of more than two or three years' standing without finding thickening of the superficial arteries.

Experimental production of arteriosclerosis by the various bacterial

[1] *Amer. Jour. Med. Sci.*, 1908, cxxxv, p. 199.

toxins affords an explanation of this gradual production of sclerosis in the chronic infections. The importance of constant absorption of such products from a chronic suppurating sinus, septic teeth or gums, a chronic colitis and so forth, cannot be over stated.

3. **Intoxications.**—Of the poisons which have an important influence on the bloodvessels, some are exogenous, others endogenous. Of the special exogenous poisons, alcohol, lead, and tobacco, the first named is very generally regarded as a potent influence in causing degeneration of the bloodvessels. In man it is very difficult to separate effects of *alcohol* from those of other causes. Of late years there has been a strong revolt against the popular belief. In France, Lancreaux rejects the evidence entirely. R. C. Cabot holds the same opinion, and it must be confessed that it is difficult in any given case to furnish evidence that alcohol alone is the cause. For example, in a middle-aged man who has drunk freely, eaten largely, and worked hard, it is impossible to say which of these factors is responsible for the degeneration of the bloodvessels. Alcohol may act either as a direct poison, causing necrosis of certain elements of the bloodvessels, or it may be a factor in maintaining a constant and high pressure.

Tobacco is another poison about which it is very difficult to get conclusive evidence. Experimentally, it is easy to produce the most extensive degeneration of the aorta in animals with nicotine. When one considers the extraordinary quantities consumed over long periods of years by men who show no trace of vascular change, or not more than the ordinary wear and tear of life would warrant, it is difficult to believe that tobacco can have a very important influence. It rapidly raises tension and may cause spasm of the arteries, which factor may account for the cases of sudden death in young or middle-aged men in whom excessive use of tobacco has been the only etiological factor. Angina pectoris is sometimes associated with abuse of tobacco, and the influence may be, as Huchard and others believe, through inducing an arteriosclerosis of the coronary arteries. A form of intermittent claudication of the lower limbs has recently been attributed to the abuse of tobacco.

Lead has long been known to have a very important effect upon the bloodvessels. A slow, gradual sclerosis is common among painters and others who take a small quantity of lead into their system. There are three elements here to be considered: the direct toxic action of lead on the bloodvessels, the disturbance of metabolism which leads to gout, and the chronic interstitial nephritis, both of which are associated with high tension and favor sclerosis. Of other exogenous poisons, tea and coffee are supposed to have an influence, but it is not easy to get conclusive evidence of the connection.

Of endogenous poisons that may promote arteriosclerosis may be mentioned all the conditions of perverted metabolism. The thickening of the arteries in gout, in diabetes, in chronic Bright's disease, in obesity, may be due to the action on the bloodvessels of poisons retained within the system. Loeper[1] has drawn attention to a number of substances,

[1] Loeper, *Arch. des mal. du Cœur.*, Paris, 1908, vol. i, p. 45.

such as oxalic acid, lactic acid and extracts of putrefying flesh, all of which produce atheroma experimentally.

4. **Conditions that Keep up High Blood Tension.**—The recent work of experimental arteriosclerosis, to be referred to later, shows the great importance of this factor in causing an arterial degeneration. Within limits, the pressure with which the blood circulates in the arteries varies very greatly, in order that the circulation may adapt itself to the varying conditions of life. Healthy individuals differ in the degree of the blood pressure, but one rarely finds it above 150 mm. Hg. The pressure varies, too, at different periods of life, and as age advances the blood pressure rises. Sir Clifford Allbutt[1] has discussed this feature in a most suggestive paper. There can be no question that in many individuals the rise in pressure antedates the appearance of the arteriosclerosis. The following are some of the causes of this heightened blood pressure: (1) *Overeating:* Excess of food and drink acts in two ways, first by keeping the bloodvessels constantly distended, and secondly, in the processes of primary and secondary metabolism substances may be formed which are directly toxic. The writer's attention has been repeatedly called to the frequency of arteriosclerosis in persons who have been temperate in every respect except at the table. It is well known to caterers that teetotallers eat much more than other people, and in the United States arteriosclerosis is very frequent among the well-to-do classes, who, as a rule, are abstemious so far as alcohol is concerned, but exceedingly careless and indulgent in the matter of eating. The writer's experience is fully in accord with that of Allbutt, that "one main cause of rising arterial pressure in middle life is excess of feeding, that is to say, of food in excess of work and excretion." The express engine capable of running fifty to sixty miles an hour if stoked for that purpose and put into the station yard to "shunt" empty cars will go to pieces very soon. This is what so many of us do with our engines. We supply the fuel for fifty miles an hour and run the engine at ten miles. In our bodies, as in the engine, damage is certain to follow from the accumulation of waste and the disproportion between intake, work done, and output. For the statement that meat eaters are more prone than others to arteriosclerosis we have no positive warrant, but the Indians and Japanese, who subsist chiefly on a vegetable diet, are said to be much less affected than Europeans.

In no way is blood pressure more surely heightened than by the persistent use of the muscles. But here, too, we must be careful not to draw hasty conclusions. A majority of laboring men have the blood pressure from 30 to 50 or 60 mm. of Hg. above that of rest during the greater part of the day. This is well within the normal limits, and cannot be hurtful. It has been determined by *x*-ray observations that calcification of the arteries of the upper limb occurs more on the side most frequently used. It is the very severe muscular efforts repeated over prolonged periods that damage the cardiovascular system, the conditions that produce the hypertrophy of the heart, as in miners, mountain climbers,

[1] *Medico-Chirurgical Society's Transactions*, vol. lxxxvi.

and athletes. The difficulty here is to separate the effect of muscular effort from associated conditions of overeating, alcohol, and tobacco. The possibility has to be considered of overactivity of the adrenals, in which an increase in the amount of the internal secretion, which keeps up vascular tone, causes hypertension and finally sclerosis. So far this is a purely hypothetical conception.

Etiologically, then, there are three great groups of arteriosclerosis: first, the *involutionary*, in which the degeneration is caused by the ordinary wear and tear of life, and which is as natural as gray hair and failing eyesight; secondly, the *toxic* group, in which the degenerations are caused directly by the poisons of acute and chronic infections and of the intoxications; thirdly, the *hyperpietic* group, in which the degeneration follows persistent high arterial tension. Practically in a given case of arteriosclerosis, in a man of, say, fifty-five, two or all three of these factors may be present, and it is exceedingly difficult to assign to each their relative value.

Pathology.—It is rare to find the arteries entirely free from disease. Even in children small flecks of atheroma or fatty degeneration of the intima are by no means uncommon. In the bodies of middle-aged persons some arterial degeneration is always present, and, as a rule, the older the individual the more pronounced they are. In extreme old age calcification may be a widespread process, but occasionally the vessels of persons above eighty years of age show very little atheroma.

While arteriosclerosis is a general disease, affecting, as a rule, all of the arteries, the process may be much more advanced in some vessels than in others. The arteries of the brain may be stiff and hard, while those of the abdominal organs show no change; or the vessels of the limbs may be stiff and rigid, while the intima of the arch is smooth. The coronary arteries may be extensively diseased in comparatively young persons, while there are no changes in the other vessels. As a rule, this limitation of the disease to the vessels of one organ or to a limited portion of the large arteries is characteristic of syphilis; but there are instances in which this disease can be excluded with reasonable certainty.

In the larger arteries, the aorta for example, the following are the important changes: (*a*) Small areas of fatty degeneration of the intima, of a yellowish color, not raised. This may be the only lesion present. (*b*) Gelatinous-looking raised areas scattered over the intima, and seen particularly about the orifices of the arteries. They are translucent, and on section are seen to be confined to the intima. (*c*) Larger plaques of yellowish color due to fusion and fatty degeneration of *b*. (*d*) Calcified plaques. (*e*) Areas of atheromatous softening, which may project above the level of the intima, and which the old writers called atheromatous pustules. (*f*) Open atheromatous ulcers, usually flat and due to the breaking down of foci of atheromatous softening. In advanced cases the inner surface of the aorta is rough and irregular from the presence of calcified plates and areas of softening. (*g*) On section of the vessel the changes are found to be chiefly in the intima, but the media is usually atrophied, sometimes with foci of necrosis and areas of calcification, sometimes of true ossification. The adventitia is thickened and

indurated, but necrosis and calcification are rarely seen in it. In many instances we find all grades and phases of the process going on side by side. The artery may be dilated, and sometimes there are small aneurismal bulgings.

Experimental arteriosclerosis, which has been studied so carefully of late years by Jores, v. Gilbert and Lyon, Fischer, Pearce, Klotz, Harvey, and others, has thrown a great deal of light upon the mode of production of the disease. Inoculation with cultures may produce proliferative changes in the media with thickenings of the intima. Diphtheria toxin, on the other hand, causes degenerative lesions affecting chiefly the media and adventitia followed by calcification. The most remarkable degenerative changes follow the use of adrenalin and other agents which raise the blood pressure. Here the media is involved, necrosis of elastic and muscle fibres takes place, with fracture and splitting of the same with early calcification. Aneurisms are formed either by direct bulgings over areas of disease of the media or from splits of the intima.

Recent researches lead to the conclusion that in the ordinary type of arteriosclerosis the primary lesion is in the media, either productive or degenerative. To compensate, a reaction occurs in the intima with hyperplasia of the subendothelial connective tissue which undergoes hyaline, fatty, and calcareous changes. According to Thoma's view, this reaction of the intima is compensatory and adaptive, tending to strengthen the wall in the spots where it is weak and to restore the original lumen of the vessel.

Despite much discussion the following changes are still unsettled. Where does the process begin? Is there a true hypertrophy of the muscle fibres? What is the relation of high tension (hyperpiesis) to the sclerosis? Which comes first? Is the primary mischief caused by the action of a toxin in the finer tissues of the capillaries and arteries? Or do these irritating substances cause spasm of the smaller vessels, and so raise the tension? What is the relation of the involutionary changes in the vessels in old age to those met with in younger persons? May not increased viscosity of the blood play an important rôle in causing high tension and arterial strain? The whole subject is in the melting pot again in consequence of the remarkable studies on experimental arteriosclerosis. We lack definite knowledge of the finer changes in the capillaries, which are probably always involved (as Gull and Sutton believed), through which, after all, the essential processes of the circulation are carried on. As age advances the smaller vessels show definite changes, chiefly in thickening of the intima and moderate hypertrophy of the other coats. Later, degeneration occurs, fatty and necrotic, particularly to the muscle cells and in the elastic fibres of the media, and calcification is common. Alterations precisely similar to this physiological arteriosclerosis may be met with in young persons, even in children, and it is pathological only in the time of life at which it has occurred. Intimal thickening in which both the elastic and connective tissue elements are concerned is perhaps the most constant feature in all types of arteriosclerosis. It may be out of all proportion to the changes in the media, and may narrow or obliterate the lumen of the vessels—*endarteritis obliterans*. This is

the most important single factor in the disease, responsible for more symptoms than all the other changes put together. It may be limited to one set of vessels, as of the legs or of the heart. The cause of this intimal thickening is much discussed. Thoma regards it as compensatory, particularly in the large vessels, but even in vessels the size of the ophthalmic artery he thinks it takes place to strengthen the vessel at a point weakened by disease of the media as illustrated in his well-known figure.[1] (See Fig. 44, p. 481.) The physiological intimal thickening as age advances is believed to strengthen the vessel weakened by senile changes in the elastic and muscular elements of the media, and in the pathological forms experimental evidence is in favor of this view.

The nature of the changes in the media and adventitia are much discussed. They probably differ in the different groups of cases. In the high tension—hyperpietic—form there appears to be an early hypertrophy of the muscular elements, as was so well described by George Johnson and more recently by Savill. It is not easy to determine this histologically, and the matter is still in dispute. The cut section of an artery contracted is very different in appearance from one relaxed, and appearances are very deceptive. This has been well pointed out by Arthur V. Meigs, whose figures of cross-sections of shrunken and unshrunken arteries show how different the coats look in the two states. In the involutionary and toxic forms, necrosis of the muscle fibres and elastic elements takes place with replacement by connective tissue, fat, or lime salts, very much as occurs in the larger vessels. The medial degeneration seems really as important in the small as in the larger arteries, and in the senile type the calcified beadings follow these necrotic changes.

Symptoms.—Arteriosclerosis disturbs function in three ways: (1) Following progressive arteriosclerosis the activity of an organ lessens and there is a gradual reduction in its capacity for work. The changes of senility are largely vascular. With a reduced blood supply the organs become less and less active, atrophy slowly but progressively comes on, and they become firmer and harder. In old age every organ and tissue in the body shows changes which may be attributed to progressive arteriosclerosis. (2) When the arteriosclerosis reaches a final and obliterative stage, if in an end vessel, atrophy follows in the territory supplied as in the arteriosclerotic kidney, or if, as so often happens, it is in the peripheral vessels of the foot or of the hand, gangrene supervenes. (3) Arteriosclerosis renders the small arteries more prone to spasm than normal vessels. The process may sometimes be studied in the vessels of the leg. The spasm is accompanied by pain, ischemia, and loss of function. The diminished volume of the pulse is readily perceptible, the foot becomes pale, at the same time there is pain, and, if at all widespread, there is muscular disability. These attacks of angiospasm are not necessarily associated with sclerosis. They may occur in normal vessels, as, for example, in Raynaud's disease, which affords many opportunities to study the effects of spasm, not only in the vessels of

[1] *Virchows Archiv*, Band cxi.

the limbs, but the transient aphasia and the mono- and hemiplegic attacks of this affection are due to loss of function in consequence of spasm of cerebral vessels. As will be mentioned shortly, in speaking of the cerebral features, precisely similar attacks occur in arteriosclerosis which may be explained in the same way. These vascular crises have been introduced to do service in explanation of a whole series of phenomena, from lead colic to angina pectoris, and from cramp of the muscles to the gastric crisis of tabes. Pal, of Vienna, in his valuable monograph on *vascular crises*,[1] gives an excellent account of the whole condition. He refers to a case of great importance as illustrating the loss of function in a part caused by transient spasm. A man, aged sixty-three years, every day, or every few days, had blindness of the right eye, lasting from a minute to several hours. Wagermann, under whose care he was, found complete amaurosis with absence of pupil reaction. The ophthalmoscopic examination showed contraction of the retinal arteries and emptiness of the veins, appearances which passed off in a few minutes with restoration of normal vision.

In so widespread a disease the clinical features will depend upon the extent to which the process has involved the arteries of different organs. So remarkable are the powers of adaptation in the body that an extreme grade may be compatible with good health. It is an every-day experience to find arteriosclerosis in persons who look well, and who are able to perform the ordinary duties of life. Sudden death may be the first and only manifestation. Rupture of a bloodvessel in the brain, thrombosis of one of the coronary arteries, rupture of a small aneurism, acute dilatation of the heart—any one of these may carry off a man in whom there has never been any suspicion of an organic lesion. Natural death, euthanasia, comes through the bloodvessels. The description in Ecclesiastes of the gradual failure of the vital powers is an epitome of the clinical features of senile arteriosclerosis. The symptoms are as varied as the organs involved. But before entering into consideration of the special features, it may be well to consider arteriosclerosis as a—

General Disease.—As already stated, there may be no symptoms of ill health, and the condition may be met with in a casual examination. In a man who has led a very energetic life, particularly if he has worked hard with his muscles, eaten much, and drunk hard, the palpable arteries are felt to be thickened, the blood pressure is heightened, there is an increase in the vigor of the cardiac impulse, the apex beat is a little dislocated outward, the first sound is thudding and prolonged, and the second is accentuated. Such a patient may look a very robust man. When present under the fortieth year, such features are always of serious, although not always of immediate significance, and it does not do to give a too unfavorable prognosis. Mental and bodily vigor of exceptional degree may persist with the most pronounced arteriosclerosis. The discovery may be a most advantageous thing, as the patient may be warned to change his method of life. A man who has been racing like the Lusitania, and in constant hazard of a breakdown, may be able to keep

[1] *Gefasskrisen*, Leipsic, 1905.

up indefinitely when the pace is reduced to ten knots an hour. An early symptom of the general disease is a slight pallor, all the more noticeable if the individual has had previously a high color. With it there may be no actual reduction in the number of red blood corpuscles. It is a question altogether of local anemia. A gradual loss of intellectual and bodily vigor is the most striking symptom. Within a few years a man may, as we say, age visibly and lose his intellectual keenness. The muscular energy is lessened and he is prematurely senile. Often the skin gets flabby and lax and the hair turns gray early. The condition is best expressed in those well-known lines of Oliver Wendell Holmes, describing the One Hoss Shay on the morning of its one hundredth anniversary:

"A general flavor of mild decay,
But nothing local. . . ."

And as in that venerable vehicle the breakdown is apt to be sudden and general. Slowly advancing, the peripheral arteries harden, the retinal vessels become more tortuous, the blood pressure rises to 150 to 200 mm. Hg., the cardiac hypertrophy becomes more marked, and the urine shows a slight amount of albumin and tube casts. Even at this stage the conditions may have been met with accidentally and the patient may be quite able to attend to his business, although conscious of failure in capacity. Very many of these patients, particularly under forty years, come to us with symptoms of neurasthenia, irritable, sleepless, and emotional. A marked lost of weight is not uncommon.

Local Manifestations.—Nervous System.—As just mentioned, the patient may present quite early all the complex and varied manifestations of neurasthenia. In the more advanced stages of the disease the cerebrospinal features are among the most important and interesting. Headache is an early and distressing symptom, associated, as a rule, with high pressure and often promptly relieved by measures which reduce it. Usually frontal and continuous, occasionally paroxysmal and resembling migraine, many patients first consult a physician for it and the real cause may be overlooked, unless careful examination is made.

Vertigo.—Transient giddiness is a very common symptom and may be one of the most distressing, although it is usually quite temporary and never with the severity or associated features of Ménière's disease. It may, however, be associated with tinnitus. It is often brought on by exertion, or follows a sudden movement, and is an accompaniment of the crises of hypertension to which some patients are subject.

Transient Monoplegias, Aphasia, and Paraplegia.—One of the extraordinary cerebrospinal manifestations is the occurrence of attacks of transitory disturbance of function of parts of the brain or of the cord, leading to hemiplegia, monoplegia, aphasia, or even paraplegia. Years ago the writer's attention was called to these occurrences in the case of a friend and colleague, a man of about forty years, with extreme arteriosclerosis. After an attack of slight palpitation of the heart, with shortness of breath, he awoke one morning of find himself unable to speak or to use his right hand. The paralysis passed away in the course of twenty-four hours, and he regained the power of speech a little more

slowly. He had a dozen or more of these transient attacks, some lasting a little longer than others, but with recovery so complete that he was able to resume his work. Once there was transient paraplegia, and for more than two days he was unable to walk. Headache was variable, not always present. The writer has seen a great many cases since, and has come to recognize it as a not very uncommon feature in arteriosclerosis of the cerebral vessels. The attacks are sudden and the recovery is complete. One patient had, within two years at least twenty attacks of transient paralysis, sometimes on one side, sometimes on the other. Although not so widely recognized as it should be, the condition has been described by many writers, particularly Peabody, Edgeworth, and others. The transitory nature, with complete recovery and the extraordinary frequency of the recurrence, put hemorrhage, embolism, and thrombosis out of the question, and the condition must be an angiospasm similar to that which produces manifestations of Raynaud's disease.

Convulsions of an epileptiform character may occur. In the absence of syphilis and of lead poisoning, convulsions occurring in middle-aged individuals should always excite the suspicion of arteriosclerosis. They are associated with high pressure, sometimes very high, and are often preceded by headache and giddiness. In Stokes-Adams disease the convulsions are attributed by some to angiospasm and arteriosclerosis of the cerebral vessels.

Progressive Dementia.—Gradual failure of the mental powers is one of the commonest symptoms of cerebral arteriosclerosis. A man begins to take less interest in his affairs, grows careless and apathetic, the memory and judgment are at fault, the facial expression is dull, and, progressing month by month, at last the psychical powers are so reduced that the individual is in a state of dementia. Apart from syphilis, in which the dementia has the well-known features of paresis, mental degeneration is not often seen as a result of arteriosclerosis in men under forty years. It is common enough as a pre-senile change in men at or about sixty years. It may be associated, too, with periods of excitement and with mental vagaries of all sorts. Rupture of the cerebral arteries leading to apoplexy and thrombosis in consequence of changes in the intima are common events in arteriosclerosis.

Cardiac.—There are three important groups of cases in which the dominant symptoms of arteriosclerosis arise from affection of the heart—the valvular, the myocardial, and the coronary.

Valvular Group.—In a considerable number of aortic and mitral valve lesions the insufficiency is due to a process in the segments identical with that which goes on in the vessels. The former is a much more important group than the latter, and a considerable proportion of all cases of aortic insufficiency in men belong to it.

Myocardial.—In general arteriosclerosis gradual failure of the hypertrophied cardiac muscle is a common and serious event, leading to the characteristic clinical picture of dilatation and progressive asystole. After a period in which the patient suffers with palpitation or violent action of the heart, he begins to get short of breath and is winded quickly

by the stairs or by a slight hill. He may awaken at night in a slight paroxysm of dyspnœa. At this period examination may show a forcible apex beat and a high-tension pulse. An attack of angina pectoris or of pulmonary œdema may occur. Soon the dyspnœa increases and the patient feels that his disability is altogether respiratory, and that if he could only get his breath he would be all right. The signs of dilatation of the heart become more marked, and there is a characteristic picture of asystole, orthopnœa, slight swelling of the feet, and cough, with, perhaps, blood-stained expectoration. The pulse is often at this stage very deceptive, as it is not always weak. The apex beat is diffuse, undulatory on palpation, and one may feel a gallop rhythm, while over the whole heart the gallop rhythm is heard on auscultation. There may be an associated systolic murmur, and the aortic second sound may still be ringing or even amphoric in tone. The state of the urine depends entirely upon the degree of venous congestion. With judicious treatment the condition may be relieved in a week or ten days, and the patient may be able to resume work. A dozen or more of such attacks may follow before the patient succumbs. Even after months of dyspnœa, recovery may take place.

Coronary Arteries.—The orifices, the main branches, or the smaller vessels may be affected. The narrowing of the orifices is a common cause of myocardial degeneration and weakness, and in young syphilitic subjects, of attacks of angina. The same may happen in any case in which the sclerosis is advanced at the root of the aorta and the orifices of the coronary arteries are seriously narrowed. Involvement of the main branches produces the same condition, but attacks of angina pectoris are more common and in a large group of cases sudden death occurs from thrombosis in one or other of the branches. In many instances of arteriosclerosis in comparatively young men the coronary arteries are involved out of all proportion to the other vessels and the attacks of myocardial weakness may precede or accompany angina pectoris, or one may be surprised to find, in a case of sudden death in a middle-aged man, who has never had any cardiac symptoms, that there is gradual fibrosis or perhaps areas of anemic necrosis are present with softening and occasionally rupture.

Renal.—There are two great groups of cases: (*a*) associated with the small contracted kidney, following an acute nephritis or coming on insidiously in gout or chronic lead poisoning, there is an extreme grade of arteriosclerosis which may be regarded as secondary and due partly to the high pressure and partly to toxemia; (*b*) the true arteriosclerotic kidney is a red, beefy organ which is firm, hard, and dark in color, not at first reduced in size, sometimes, indeed, slightly enlarged. Very often, with this kidney, there may be few or no urinary symptoms. In a late stage there may be large, flat areas of atrophy of the cortex, or a large section of one organ may be involved in consequence of an obliteration of the arteries passing to the part.

The *urine* in these two groups of cases present, as a rule, striking differences. In the small contracted kidney the amount is increased, the specific gravity is very low, the albumin small in amount, often

absent in the morning, hyaline casts are present, and very often red blood corpuscles. The urine of the arteriosclerotic kidney may contain at first no albumin, or, if present, the amount is not large, the specific gravity is normal or sometimes high. Later, the albumin may be large in amount and sometimes, as when a patient is admitted with an attack of cardiac dilatation, the urine is scanty with large amount of albumin and numerous tube casts, due to an acute intercurrent nephritis.

Abdominal.—Much attention has been paid of late years to abdominal symptoms in arteriosclerosis. Pal and others believe that very many of the painful gastric and intestinal conditions are associated with spasm in the gastric and mesenteric vessels; some would associate the multiple functional disturbances of abdominal neurasthenia with degenerative changes in the arteries. Certainly one may see a sclerosis of the mesenteric vessels far in advance of that in other vascular territories, but the writer does not know that we are yet in a position to say that any definite symptoms are connected with it. Ulcer has been met with in connection with endarteritis of the smaller vessels of the stomach. The victims of angina pectoris may have marked abdominal symptoms, and of late writers have spoken of such attacks of abdominal pain as *angina abdominis*. This is really an old story, as years ago Leared described "a disguised disease in which the heart affection was so masked by that of the stomach that nothing in the statements of the patient had any bearing on the primary disease." A number of these cases have come under my observation, but even when the pain is entirely abdominal the general features have usually been sufficient to make a diagnosis.

Milder attacks of epigastric pain and intestinal cramp and meteorism have been attributed to arteriosclerosis. The clinical features of gastric and intestinal dyspnœa have been regarded as manifestations of circulatory disturbance in the sclerotic vessels. One cannot read the literature on the subject without feeling that the writers have often been carried away with theoretical considerations. An intermittent claudication of the stomach has been described.

Peripheral Arteries.—A few among the many manifestations following sclerosis of the arteries of the limbs may be considered:

Cramps of the Muscles.—Local tetanus (cramp) in a muscle follows overexertion or a sudden prolonged effort in a strained or unaccustomed position. Long-distance runners are very subject to cramp in the calves of the legs, and sustained use of any group of muscles may throw not the whole group, but some portion, into strong tetanic cramp. This form and the commoner variety, which results from strained posture, are met with in young and old, but in the latter there is a form of great interest, and often very troublesome, which is probably associated with arteriosclerosis. Few elderly persons escape attacks of cramp, chiefly nocturnal and sometimes of such severity that the condition requires treatment. It is more common in persons of dull habit and of what we call a gouty disposition—*i. e.*, persons who eat too much and work too little; but attacks may occur in thin, abstemious persons. It is difficult to connect the condition definitely with angiospasm, but the writer has so often found marked sclerosis of the palpable vessels of the legs, or

absence of the pulse in the dorsal arteries of the feet, that he has come to regard the bad nocturnal attacks in elderly persons as a manifestation of endarteritis. Twice attacks of the most dreadful agony have been seen, recurring every few minutes in the muscles of the legs, knotting them in places into hard lumps which took a minute or two to disappear. In one old woman they were so severe that only large doses of opium gave relief. In both these patients the pulse could not be felt in the feet. Ligation of an artery may throw the muscles into a spasm, and the sudden tap on the facial artery may cause tetany of the muscles, so that it is not impossible that angiospasm (a vascular crisis) may be responsible for these painful cramps in elderly persons.

Neuritic Pains—Erythromelalgia.—In connection with endarteritis obliterans of the vessels of the legs, numbness, tingling, burning, and shooting pains are common complaints. In diabetes a whole group of neuritic symptoms may precede the local gangrene of the toes, and the same may occur before senile gangrene. In erythromelalgia, the red painful neuralgia, arteritis obliterans has been found in many cases. And there is a very interesting group of cases of idiopathic endarteritis of the vessels of the legs, in which in comparatively young men, without any history of syphilis, pains precede the occurrence of the severe obstructive manifestations.

Intermittent Claudication.—In the cases in the horse, described by Bouley and in Charcot's original case in man, the vascular obstruction was aneurismal. To Erb we owe the recognition of the frequency of this symptom in arteriosclerosis of the vessels of the legs. It is a question of a due balance between a supply of energy through the blood and muscular expenditure, as Allan Burns puts it in his original explanation (1809). There are cases with neuritic pains and well-marked signs of vascular disease, palpable vessels, spasm of the arteries, with pallor of the feet in exertion, or absence of pulsation in the dorsal arteries of the feet. In others, the signs of arterial disease are not so clear, and it is possible that there may be an angiospastic form; or it may be in some cases, as Déjerine suggests, an affair of the spinal arteries with anemia of the cord. In the majority of the cases seen by the writer, the arteriosclerosis has been pronounced. It is not always a cramp-like pain that causes the limping or claudication, but there may be a relaxation of the limbs, a giving way for a few seconds, or, without actual falling, an inability to make any further effort. The relation of arteriosclerosis of the peripheral arteries, to gangrene, erythromelalgia, scleroderma, etc., will be considered in other sections.

Diagnosis.—To the rule that the disease is uniformly distributed in the body there are many exceptions. The most widespread peripheral arteriosclerosis may exist with a moderate grade of disease of the aorta. On the other hand, the endarteritis deformans of the latter vessel may be out of all proportion to the disease in the smaller arteries. The vessels of the head, of the heart, or of the kidneys may be in an advanced stage of sclerosis, without any change in the palpable arteries. The most serious form is that in which the smaller vessels are chiefly affected and which comes on in middle life or in young persons.

From the appearance of the individual not much may be determined. To no condition is Shakespeare's remark more applicable—"the outward shows may be least themselves." A robust, vigorous looking man in the prime of life may have vessels in the most advanced stage of sclerosis. While there are patients who present a pronounced anemia, the florid cardiovascular facies is the more common. The active muscular business man of forty-five years, who all his life has never had to spare himself, and who has prided himself on his "fitness" for everything, is shocked to find that there is something wrong with the machine; or to the young-old man who has reached the grand climacteric without a day's illness, Nemesis whispers "time is up." In other instances a remarkable change takes place in a few months. Following, perhaps, a domestic shock or a financial crisis, in other instances without any obvious cause, a man begins to fail. The elasticity and firmness go from the gait, the movements become less active, there is loss in weight, and the intellect is impaired, as shown in absence of initiative and incapacity for continuous work. So rapid may be the breakdown that some of these instances of pre-senile arteriosclerosis may be termed acute. Too much stress must not be laid upon certain features usually regarded as indicative of degeneration. Early graying of the hair may have nothing whatever to do with arteriosclerosis, and in my experience it has not been a common accompaniment. Nor is the arcus senilis of much value as an indication. It may occur in middle-aged men with perfectly good arteries, and it has not been in my experience a special feature in early arteriosclerosis.

The cardinal points in a case of arteriosclerosis are usually well marked: (1) thickening of the peripheral vessels; (2) signs of hypertrophy of the left ventricle, shown by the apex beat dislocated outward, the thudding first sound, and the accentuated aortic second; (3) heightened blood pressure; (4) a slight and variable amount of albumin in the urine. As a rule, this quartet of symptoms is present in a large proportion of the patients when first they come under our observation. At this stage the damage is done. The important point for the practitioner is to learn to recognize the early stages when there is a reasonable chance that the progress may be arrested. We can form a pretty clear judgment of the state of the arteries and the general physics of the circulation by sight, by touch, by estimation of the blood pressure, and by the study of the pulse.

When at all advanced, the superficial arteries of the body become visible and tortuous. This is particularly well seen in the temporals, which, as age advances, stand out as prominent, tortuous, even beaded cords. One must learn not to mistake a full for a sclerotic vessel. When the peripheral circulation is relaxed, as in high external temperatures or during excitement, the superficial arteries become prominent. When the sclerosis is at all advanced the brachials stand out markedly sinuous and throbbing visibly. The radials and ulnars, the external iliac just above Poupart's ligament, the femorals just below, and the dorsal arteries of the feet may all be visible. Of all vessels in which to see early thickening, the retinal arteries are the most important. de Schweinitz in par-

ticular has called attention to the great importance of its early recognition by the ophthalmoscope. Not only may it be readily seen that the arteries are thicker than normal and more tortuous, but the way in which they cut across the larger veins is very distinctive. A small hemorrhage may sometimes be seen.

By *palpation* we are enabled to judge with fair accuracy of the degree of thickening of the vessel wall. It requires not only experience, but education, to form a correct judgment on the state of the arteries. A perfectly normal vessel, when contracted, may feel hard and cord-like. On the other hand, in a radial definitely thickened, but in a state of extreme relaxation, the hardening of the walls may escape detection. The state of the tissues about the artery, the amount of fat in the skin, the size and fulness of the veins—all have to be considered. One of the commonest of mistakes is to regard as thickened any vessel one can roll under the finger. But in a state of very high tension and if very full, the arterial tube may feel cord-like. To estimate the presence of sclerosis it is not sufficient to examine the radials and temporals, but the brachials and femorals should also be felt, and palpation should be made, first, in the natural condition; secondly, the artery should be felt below a point where the pulse wave is obliterated; and thirdly, a small section of the vessel should be emptied of blood and palpation made between the two points of pressure. It may only be in this last way that a true opinion can be formed of the existence of sclerosis. It does not do simply to obliterate the pulse and feel immediately below it, because in conditions of very high tension, in the radial and temporal arteries for example, the recurring pulse appears beyond the point of pressure. In the superficial arteries, as the radial, the finger is able to appreciate four distinct grades: (1) the normal vessel wall, which in a moderately thin wrist may be first differentiated from the adjacent tissues; in the cold, or if hand has been placed in ice-cold water the tightly contracted artery may be felt as a fine cord; (2) moderate sclerosis in which the vessel is readily felt and in which, after the blood has been pressed out of the artery, there is a definite tubular cord; (3) extreme sclerosis in which the radial is felt like a piece of whipcord, firm, hard, incompressible, rolling under the finger, and presenting little or no difference in the sensation with the blood in or out of the vessel; (4) calcification, which in the radial is easily felt, ringed or beaded.

The introduction of instruments for measuring blood pressure has given us one important means of estimating accurately the condition of a subject of arteriosclerosis. Early in the disease, or before the thickening of the vessel is evident, the blood pressure may be persistently high. This *presclerotic stage*, as it has been called, is important to recognize, and yet it is only exceptionally that we are able to trace all the stages in a given patient. More commonly the high pressure and sclerosis are coexistent, but there is no definite parallel between the two processes. The very highest pressures, above 250 mm. Hg., may be present with quite moderate thickening of the vessels. On the other hand, low blood pressures may coexist with early arteriosclerosis, or following an acute illness, dilatation of the heart, a shock, or certain

complications, such as pulmonary œdema, and in the late stages of the intercurrent affections.

The character of the *pulse* in arteriosclerosis is best described as hard and resistant, and the vessel is plainly perceptible to the finger in the intervals of the beats. As already mentioned, it is important to recognize the difference between the hard sensation conveyed to the finger by a high-tension pulse and that conveyed by stiffening of the walls. The two may coexist, but the former may give the deceptive sensation of a permanent cord to the artery. Usually, too, the pulse is incompressible, or, more correctly, is difficult to compress. One can always obliterate the pulse wave in the radial, but it quite commonly happens that, in spite of the firmest pressure, the pulsation may be felt beyond the finger. This is a recurrent pulse through the superficialis volæ, and it may be at once checked by compressing the ulnar artery. It is present frequently in high tension, but it is just as common when the smaller arterioles are greatly relaxed and the peripheral tension low. To estimate the state of the vessel wall in a high-tension pulse, obliterate the radial artery close to the metacarpal bone, then with the index finger of the other hand press the blood out of a section of the radial, compress it, and then, with the middle finger, feel the empty vessel. If very sclerotic, it will be almost as prominent empty as full. But when the cord-like sensation is due to a high pressure only, there may be very little sensation given to the finger by the vessel wall itself. The sphygmographic tracing of the high-tension pulse is very characteristic, with a wave of moderate height, a sloping ascent, and a delayed decline with a little or no dicrotic wave.

Treatment.—Once degeneration, fibrosis, and calcification have taken place, the damage is irreparable, and as "all the King's horses and all the King's men could not put Humpty Dumpty up" after his fall, so all the hygienic, dietetic, and medicinal measures cannot restore the normal structure of the arteries. But this does not mean that the condition is always hopeless. Much may be done to prevent the sclerosis increasing and much may be done to relieve symptoms.

The treatment may be carried out along the following lines, varying, of course, with the individual cases:

General.—The patient should be urged to live as peaceful a life as possible, cutting off all sources of mental strain and worry. A protracted holiday may be most helpful. It is not wise, as a rule, to urge a man to give up work entirely. Too often this is followed by a neurasthenic breakdown. The most difficult part of the treatment is so to arrange a man's life that he may have moderation in work. So long as it can be lightened, there is no reason why he should not continue. Of course, when there are signs of cardiac failure or any pronounced local features, or if the mental changes are marked, it would be wise to urge complete rest. These patients often require the consolation of sensible advice. On hearing that they have hardening of the arteries, many men with years of useful life before them are inclined to throw up the sponge at once. When of moderate extent in a man aged forty-five or fifty years, it may not lessen the expectation of life by more than five or six years.

The writer has several arteriosclerotic friends in whom the condition was recognized more than twenty years ago. One old patient, who returned from a visit to London in 1881, was prepared to give up everything because of his arteriocapillary fibrosis. The fright was the best thing that ever happened to him, as he lowered sail and has been going on very comfortably doing a fair amount of work.

Exercise.—Golf, horseback riding, walking, bicycling, all in moderation, are advantageous. Allbutt recommends cautious hill climbing. The relaxation of the vessels of the skin and of the peripheral arteries generally which follows moderate exercise lowers the blood tension and relieves the heart. All sudden effort likely to throw a strain upon the vessels should be avoided. The action of the skin should be promoted by a daily bath. In the winter it is best taken at night and warm. An occasional Turkish bath, with a good rub, is helpful.

Food.—The one essential factor in the diet of arteriosclerotic patients is reduction in the amount. He should be taught gradually to reduce the quantity of food until he finds the minimum on which he can maintain the mental and bodily vigor. He will often be surprised to find that it is one-third or one-fourth of that which he has been in the habit of taking. He may take a cup of tea, a boiled egg, and a couple of slices of toast for breakfast; a vegetable soup with a rice pudding for luncheon; a piece of fish, a couple of vegetables, and stewed fruit for dinner, with a glass of hot milk at night, or a bowl of bread and milk. With a diet along these lines an arteriosclerotic may successfully pray the prayer of Hezekiah, and get, like him, a fifteen years' extension. He can do without meat perfectly well. Oysters, eggs in moderation, and fish may be taken with plenty of fruit, vegetables, plenty of bread and butter, and milk. It does not seem that we need dread specially the injurious effects of the lime salts which are abundant in milk and in eggs. Buttermilk is an excellent and easily digested food, even when milk is not. Sour milk has been a favorite drink with many persons who have lived to a very advanced age, like Thomas Parr, and in this connection it is interesting to note the strong opinion of Metchnikoff as to the value of the lactic acid products in preventing abnormal processes of fermentation in the large intestine. Spirits of all sorts should be given up. Tea and coffee may be taken in moderation. A man who has been a heavy smoker should reduce his allowance to two or three cigars a day.

Removal of Toxins.—Any possible source of these should be remedied. The mouth should be carefully examined, any defective teeth being remedied or removed and pyorrhœa alveolaris rigorously treated. Inquiry should be made for any syphilitic taint and specific treatment given if necessary. A Wassermann test would eliminate those cases certainly due to syphilis.

Medicinal Treatment.—Of remedies believed to have an influence directly upon the coats of the vessel, only iodide of potassium is of value. It is stated that, experimentally, arteriosclerosis may be prevented if, coincidently with adrenalin, iodide of potassium is given to the animal. In all syphilitic cases it should be used freely, and even in the early stages the drug should be administered in moderate doses,

15 to 20 grains (gm. 1 to 1.3) three times a day, and kept up for some months.

The blood pressure is much more efficiently lowered by dieting and mode of life than in any other way. Of the drugs which have an influence, the nitrites are the most important. The commonly used nitroglycerin is often effective, but rarely given in large enough doses, and even then is apt to be very transient in its effect. It is best given in solution freshly made, and the patient may take from 1 to 3, 4, or 5 minims of the 1 per cent. solution three or four times a day. In crises of high tension larger doses may be given. It does not seem to do any harm, and individuals react so differently to the drug, that it is well always to test it upon each patient. We often do not get good results until much larger doses are given than those usually employed. The sodium nitrite, in 1 to 4 grain (gm. 0.06 to 0.25) doses every three or four hours, has a somewhat more permanent action and is often of very great service. Erythrol tetranitrate in doses of gr. $\frac{1}{4}$ to ii (0.015 to 0.13), has a still more prolonged action.

Arsenic in small doses is helpful, particularly in the cases with early anemia. One difficulty which everyone has experienced is to keep the blood pressure low by means of drugs; the reduction is temporary, and very soon the instrument records pressures as high as ever. In the crises of hypertension brisk saline cathartics are most helpful. In any case it is well to bear in mind that the only valuable measures for permenent reduction of blood pressure are the hygienic and dietetic. The treatment of the various complications of arteriosclerosis are dealt with in the other sections on diseases of the heart, kidneys, etc.

POLYARTERITIS ACUTA NODOSA (PERIARTERITIS NODOSA).

In 1866, Kussmaul and Maier reported a case of a man, aged twenty-seven years, who had an acute, progressive "chlorotic marasmus" with fever and tenderness of the skin and muscles. Hard, bead-like nodules were present in the skin of the thorax and abdomen, which were afterward found to be thickening of the subcutaneous arteries. The case was thought to be one of trichinosis. Postmortem, little aneurisms were found on almost all of the smaller arteries of the body. These were believed to be due to inflammatory infiltration of the adventitia, and they gave the name *periarteritis nodosa*. Since then other cases have been recorded. A full abstract of each is given by Dickson.[1] Only three of the patients were females. The arteries of the heart, the kidneys, mesentery, and the liver were attacked in all the cases. The physical features depend a good deal upon the vessels affected. The onset is, as a rule, sudden and there is moderate fever throughout. Weakness, hyperesthesia, pains in the muscles, anesthesia, and anemia are marked symptoms. Vomiting and diarrhœa are common. Headache, excitement, convulsions, optic neuritis, and paralysis may be present when the cerebral vessels are involved. The diagnosis has rarely been made; the

[1] *Journal of Pathology*, 1907, vol. xii, No. 1.

condition is usually mistaken for meningitis or typhoid fever. A remarkable case was admitted to my ward in 1901, and is reported by Sabin:[1] The patient was a woman, aged thirty-two years, who had had dilatation and vomiting with emaciation and areas of anesthesia; she looked very ill and had been confined to bed for five weeks. There was an extreme grade of annular sclerosis of the arteries, numerous subcutaneous hard nodules were scattered over the abdomen, just such as were present in the case of Kussmaul and Maier. The case was very similar in many respects to the one reported by H. M. Fletcher.

Nothing is known as to the etiology of the disease. Bacteria have not been found. The earliest lesion apparently is a destruction of the muscular coat with the giving way of the internal elastic lamina of adventitia leading to aneurismal dilatation. Dickson thinks that there is a primary periarteritis established, involving the vasa vasorum. The little nodular bodies may be present in enormous numbers. Many of the little aneurisms are filled with thrombi. The condition differs entirely and must be distinguished from nodular periarteritis of syphilis.

[1] *Johns Hopkins Hospital Bulletin*, 1901, vol. xii, p. 195.

CHAPTER XII.

ANEURISM.

By Sir WILLIAM OSLER, Bart., M.D., F.R.S.

Definition.—A tumor containing blood in direct connection with the cavity of the heart, the surface of a valve, or the lumen of an artery.[1]

Classification.—It is not easy to make a satisfactory division of the various forms of aneurism. The following will be found a useful one for practical purposes:

1. *True aneurism* (A. verum, A. spontaneum), in which one or more of the coats of the artery form the walls of the tumor.

(*a*) *Dilatation aneurism.*

1. Limited to a certain portion of a vessel—fusiform aneurism, cylindroid aneurism.
2. Extending over a whole artery and its branches—cirsoid aneurism.

(*b*) *Circumscribed saccular aneurism*—the common form in the aorta in which there is distension of two or more of the coats, or of the adventitia after destruction of the intima and media.

(*c*) *Dissecting Aneurism,* with splitting of the coats to a greater or less extent and occasionally with the formation of a new tube lined with intimal endothelium.

2. *False aneurism,* following wound or rupture of an artery, causing a diffuse or circumscribed hematoma.

3. *Arteriovenous aneurism*—communication between artery and vein, either direct—aneurismal varix—or with the intervention of a sac—varicose aneurism.

4. *Special forms,* such as the traction aneurism, the erosion and parasitic forms, which have a pathological rather than a clinical interest.

Etiology and Pathology.—Incidence.—That the number of aneurisms differs in different localities has long been recognized. In Vienna, von Schroetter states that of 19,300 postmortems in ten years, there were only 230 aneurisms. Eppinger found only 22 in 3149 postmortems. At St. Bartholomew's Hospital, during thirty years, there were 631 patients with aneurism. At Guy's Hospital, between 1854 and 1900, there were 18,678 necropsies, with 325 cases of aneurism. There were 1078 deaths from aneurism in 1905 in England and Wales. The statement is usually made that it is more common in Great Britain and Ireland than on the Continent.

[1] It is not possible to frame a definition to include every condition which we now speak of as aneurism. For example dilatation of the aorta, the uniform enlargement of arteries of the third and fourth dimension, and the abnormal communication between vessels are not within this definition.

Age.—The large statistics of Crisp, 555 cases of aneurism in different situations, show the greatest frequency to be between the ages of thirty and forty years, 198 cases; between forty and fifty, 129. With this the statistics of Lebert and of Liddell accord, and it is of importance as showing that the incidence of the disease is below the age at which arteriosclerosis is met with. Of the 898 deaths from aneurism in males in England and Wales in 1905, 462 occurred between the thirty-fifth and fifty-fifth years. It may occur at any age. Jacobi and, more recently, Le Boutillier[1] collected the statistics of aneurism in the young. The latter found in the literature 80 cases in persons under twenty years of age; only 14 were under twelve years of age, and the youngest was in a child of two. Eighteen of the cases were of the thoracic aorta, 5 of the abdominal. In the very young, congenital syphilis plays an important part, as in the remarkable case reported by Wilson and Marcy in a child aged four years with extensive arterial disease and a large aneurism of the arch of the aorta. In the peripheral vessels the aneurisms are often of embolic origin. In extreme old age latent aneurism is not uncommon, either in the form of the dilatation of the arch or of small, saccular pouching of an atheromatous aorta.

Sex.—In Crisp's statistics the ratio of males to females was 5 to 1, and this is a fair average for aneurisms of all sorts. In 1905, 898 males and 188 females died of aneurism in England and Wales.

Occupation.—Hard workers, the strikers in foundries, the dock workers, soldiers, sailors, and the very muscular and robust men are chiefly affected, but the disease may occur in feeble individuals who have never worked hard with their muscles. For years it has been known that soldiers were peculiarly liable to the disease, and the studies of Myers, Welch, and others called attention to the great frequency of aneurism in the British army. This reputation is still maintained. The figures given for the British army (1905) home contingent, strength 118,224, show 18 deaths from aneurism. In Germany (1904 to 1905), with a strength of 555,777, there were 4 cases of aneurism; and in Italy (1903), with a strength of 206,468, there were 6 cases of aneurism. The high percentage in the British army is undoubtedly associated with the great prevalence of syphilis. For the year ending September, 1900, the incidence of syphilis in the German army was 18.5 pro mille; in the Austrian, 64 pro mille; and in the English, 122.4 pro mille. In the British navy the figures for five years, as sent by Sir Herbert Ellis, Director General, are as follows: 1902, force 99,600, cases 16; 1903, force 103,100, cases 23; 1904, force 110,570, cases 13; 1905, force 111,020, cases 22; 1906, force 108,190, cases 29. Bassett-Smith calls attention to the frequency of aneurism at the Naval Hospital, Haslar—47 cases in seven years.

Race.—The Anglo-Saxon is stated to be more subject to the disease. The statistics of Guy's Hospital and of the Vienna General Hospital quoted above show a decidedly greater proportion in London. In the United States of America aneurism is common among the working

[1] *Amer. Jour. Med. Sci.*, 1903, vol. cxxv, p. 778.

classes. It is more frequent among the negroes of the Southern States. In the wards for colored patients at the Johns Hopkins Hospital arterial disease and aneurism were relatively much more common than in the wards for the whites. The figures relating to aneurism are as follows: Of 345 admissions to the medical wards for aneurism, 213 were white and 132 colored (the proportion of total admissions of white to colored is about 4 to 1).

Determining Causes. The determining causes of aneurism of the aorta are three: First, poisons which lead to changes in the coats of the vessel; second, conditions which increase and keep up the arterial tension; and third, internal trauma, the strain of muscular effort, particularly in the fourth decade, when the vital rubber begins to lose its elasticity.

Among the most potent poisons in causing arterial changes are those of the acute infections, and among these the first rank is taken by *syphilis*. Someone has well remarked that "Venus loves the arteries." The older writers, particularly Paré, Lancisi, and Morgagni, knew of the close association of lues and aneurism. Among modern writers the connection was referred to incidentally, but it is only a little more than a quarter of a century since investigations have shown the remarkably high percentage of syphilis among subjects of the disease. In his well-known investigation,[1] Francis H. Welch, of the British army, found that 66 per cent. of his series had had syphilis. He described very clearly, too, the macroscopic changes in the aorta, particularly the cicatricial-like puckering of the intima. The constriction of the clothing and the temporary forced exercise he regarded as secondary elements. It is notorious that a history of infection, even in persons with well-marked signs of the disease, in not easy to get, particularly in women. There are a great many cases in which syphilis is latent, but the more closely the question is looked into the more one becomes impressed with the importance of lues as the essential factor in the causation of aneurism in persons under forty-five years of age.

The recent studies of Heller, Döhle, Chiari, and Benda have confirmed the views of Köster, that the primary change is in the media, and there is now very generally recognized a syphilitic aortitis with definite characteristics. Macroscopically, it may be limited in extent, localized at the root of the aorta, or about the orifice of an aneurism, or there is a band of an inch in width on some portion of the tube, while other parts of the aorta and its branches are normal. In other instances the intima is involved, not with the usual plaque-like areas of atheroma, but there are shallow depressions of a bluish tint and short transverse or longitudinal puckerings, sometimes with a stellate arrangement; or the intima is pitted and scarred with small depressions and linear sulci. Microscopically the most important changes are found in the media and adventitia: (*a*) perivascular infiltration of the vasa vasorum; (*b*) small-celled infiltration in areas of the media, with (*c*) splitting, separation, and destruction of elastic fibres and the muscle cells. The process

[1] *Medico-Chirurgical Society's Transactions*, 1876.

is largely a productive mesaortitis, and so marked may be the foci in the adventitia and media that they look like miliary gummata, and, in fact, were so described as far back as 1877 by Laveran and by Heiberg. The intima over these areas may be perfectly normal, but it often shows signs of thickening with fatty degeneration and the production of hyaline. Similar changes have been described in the larger bloodvessels in cases of congenital syphilis by Weissner, Bruhns, and Klotz. And lastly, the specific nature of this mesaortitis has been determined by the detection of the spirocheta pallida.

The experimental production of aneurism bears out this view. The high pressure caused by injection of adrenalin produces a fracture and separation of the elastic fibres of the media, and over these areas where the wall is weakened the intima may split with the formation of a localized aneurism, sacculated or dissecting, or the intima may gradually yield without actual rupture.

The following are among the important features of syphilitic aneurism: It occurs, as a rule, in persons under forty; the ascending arch is most apt to be involved; angina pectoris may be an early symptom; aortic insufficiency is often associated with it; the aneurisms are frequently multiple, five, seven, and nine have been described; the small cup-formed sacs, of which there may be four or five in the ascending arch, are almost always syphilitic; other luetic features may be present, gummata of the liver or bones; there are signs of locomotor ataxia or the husband may have tabes and the wife aneurism, or, as in a case reported by Jaccoud, both husband and wife have aneurism; in a large proportion of cases the Wassermann reaction is postive; and lastly, antisyphilitic remedies may relieve the symptoms.

Other acute infections play a less important rôle. There are two ways in which aneurism may be associated with the specific fevers. In any one of them local spots of degeneration, usually of the intima, may occur, or patches of mesaortitis may develop, leading to a weakening of the wall. Thayer and others have shown the frequency of these changes after *typhoid fever,* and the same may happen after *influenza, pneumonia, erysipelas,* and *scarlet fever;* there is doubt about *malaria,* upon which some of the French writers lay stress. The other way is associated with the *endocarditis* of the specific fevers. Direct extension to the aorta from vegetations on the valves may take place, but more frequently the process is embolic, with patches of mesaortitis over which the intima rupture, just as occurs in the experimental production of aneurism. In the aortitis of *rheumatic fever* one or other of these forms may be followed by aneurism; but many of the cases described as aneurism of the aorta in this disease are instances of the dynamic dilatation associated with aortic insufficiency and a huge left ventricle. But true aneurism does occur. In a case reported by Renon, the patient, aged sixteen years, developed signs of aneurism very rapidly with aortic insufficiency in the course of rheumatic fever. Death occurred from hemorrhage. The difficulty in the diagnosis of these cases will be referred to later. The type arising in the acute infections will be considered in a special section on mycotic and embolic aneurisms.

Tuberculosis is frequently met with as a complication of aneurism, 25 to 29 per cent. (Soltau Fenwick), but it plays a very minor part in the etiology, except of the erosion form occurring in tuberculous cavities in the lungs. The aorta or one of its main branches may be eroded from without by a tuberculous gland with the formation of an aneurism.

Intoxications.—Alcohol favors arterial degeneration perhaps directly, but more often indirectly, as one of the causes of permanent high tension. It is one of the three factors which make aneurism common among the laboring classes, although it plays a minor rôle in comparison with syphilis and hard work. There are some statistics, those of Etienne for example, which give a very low percentage of history of alcoholism—only 28 among 240 cases. *Tobacco* which has been shown experimentally to have an important influence in causing arterial degeneration, cannot be said to play any part in the etiology of aneurism. *Lead* has, in man, a decided action in causing degeneration of the arteries and in this way predisposes to aneurism.

All conditions which favor an excess or a retention in the system of the waste products of nutrition lead to arterial degeneration, and in a few cases to aneurism, but the causes of arteriosclerosis and of aneurism are by no means identical.

Embolism as a Cause of Aneurism.—In 1888 a man died in the Montreal General Hospital with fever and signs of aortic insufficiency and aneurism. The postmortem revealed an extraordinary condition—acute endocarditis of the aortic segments, with five aneurisms in the arch of the aorta. The largest of them, the size of a billiard ball, projecting to the right just above the aortic ring, was very thin-walled and had numerous greenish vegetations on its lining wall, which at one point had perforated into the pericardium. The intima of the aorta was smooth, and on the arch above the larger aneurism were three small ones not larger than cherries. From the side of the intima they were not visible, but their site was indicated by the pressure of small, fungoid outgrowths. These were seen on the edges of narrowed slits of the intima which led directly into the small, saccular aneurism. This was the first instance in which the *mycotic* character of this type of aneurism was recognized. It has since been studied very carefully by numerous observers.

There are two modes of formation: (*a*) In the smaller vessels the condition, as described by Ponfick and by Pel, is due to the direct lodgement of emboli with infection and erosion of the wall and the production of an aneurism. A number may occur in different vessels. Libman reports a case with four aneurisms on the mesenteric vessels, a fifth on the right branch of the hepatic artery, a large one on the right femoral, and before death, right hemiplegia with aphasia probably from rupture of a mycotic aneurism of the left sylvian artery. In another case of Libman's, with mitral and aortic endocarditis, a mycotic aneurism of the left femoral artery perforated the vein with the formation of an arteriovenous aneurism. In this form there is no question of the direct local infection of the intima by the emboli.

(*b*) In the case of the *multiple mycotic aneurisms* of the aorta, it is a different matter. Here, in all probability, the emboli pass to the vasa

vasorum and cause a mesaortitis with weakening of the wall. The intima splits, and in this way a small aneurism is formed. In the case reported by the writer, and in other instances, particularly the one reported by John McCrae,[1] splits in the aorta were sharp and defined as if made with a knife. There may be no disease of the intima itself in the neighborhood. With this view Eppinger concurs, and he remarks that the multiplicity of the lesions within a small radius is evidence of the embolic nature. In other instances there is a verrucose aortitis which has extended directly from the valves and is not of an embolic nature; and in a few rare instances this occurs in rheumatic fever. Embolic aneurisms are not always mycotic. A fragment from a calcified vegetation dislodged into the circulation may lacerate the intima at the point of lodgement with the formation of a traumatic aneurism. The writer saw a remarkable case of this kind in the Radcliffe Infirmary with Dr. Mallam: A man with aortic insufficiency and a remarkable musical diastolic murmur, had been under observation for a long time, and had frequently been used for examination purposes. Suddenly one day he had an agonizing pain in the calf of one leg, which became swollen, hot, and painful. As the swelling subsided a pulsation was noticed, and he recovered in a few weeks with a well-marked aneurism of the posterior tibial artery. The musical quality of the diastolic murmur disappeared entirely. No doubt a small calcified spike at the edge of one valve had been dislodged. A large majority of the cases occur in connection with ulcerative endocarditis. Pain of an agonizing character is present in the area where the emboli lodges. Periarteritis, swelling, and infiltration of the surrounding tissues usually occur, and it may not be until their subsidence the the pulsation is noticed.

Relation of Aneurism to Atheroma.—Everyone who has made many postmortems, particularly in very old people, must have been struck with the fact that the extent of atheroma bears no relation whatever to the frequency of aneurism. The aorta may be a calcified tube, with an intima as rough as the skin of a crocodile, without the presence of aneurism. The truth is the *endarteritis deformans* of Virchow is not necessarily associated with weakness of the media and adventitia. Chiari made a careful comparison between a series of cases of ordinary atheroma of the aorta and of mesaortitis. Of his conclusion, which has special importance in the differentiation of these two groups, a summary may be quoted: "In atheroma he found a primary change in the intima, a thickening with a tendency to hyaline, mucoid, or fatty degenerations, leading to necrosis or calcification. In the early stages the media and adventitia appeared normal. In the later stages changes similar to those in the intima appeared in the inner layers of the media, while the outer layers showed proliferation of the vasa vasorum with small-celled infiltration around them, and in the adventitia there was in some cases considerable infiltration around the vasa vasorum, the walls of which showed some degree of proliferating endarteritis. These inflammatory changes, however, remained localized, and even in advanced cases

[1] *Journal of Pathology and Bacteriology*, 1905, vol. x, p. 373.

did not reach a very great degree of intensity. Only by the actual pressure of a large calcareous patch was the media destroyed to any great extent. He considered that such a condition could be produced by any injury to the vessel, infections or intoxications, or the disturbance of nutrition which accompanies old age" (abstract by C. N. Aitchison, M.B.[1]). In other groups the change was a mesaortitis in syphilitics or the subjects of general paralysis and the intima presented the furrows and scars already described.

High Blood Pressure.—Next to destruction of the elastic fibres of the media by a mesaortitis this is the most important single factor in the causation of aneurism. It acts in two ways: if permanent it leads to arteriosclerosis and weakening of the media, so that there is dilatation, either diffuse of the aortic arch or in spots. More important still is the sudden increase of tension following a rapid movement or severe strain, as in lifting, jumping, or the straining movements at stool or in the act of parturition. Here the danger is that by an internal trauma over the weakened media the intima may tear with the formation of a small sac. The process may be traced in the production of *experimental* aneurism. With adrenalin, tobacco, and bacterial poisons, extensive degeneration of the aorta and larger vessels is caused, but what is most interesting in this connection is the formation of aneurisms, either (1) multiple bulgings in areas in which the media is greatly weakened, causing pouch-like aneurisms, just such as we see in the endarteritis deformans of old people; or (2) the normal-looking intima is split over an area of mesaortitis, a clean-cut, knife-like incision, beyond which is a little saccular dilatation or the beginning of a dissecting aneurism. These splits of the intima over local areas of degeneration, are identical with those met with in the human aorta.

External trauma has a definite influence on the causation of aneurism. Vesalius noted this in one of his cases. Many instances have followed blows on the chest, falls, or the jar of any accident. While rupture of the healthy aorta may occur in these cases it is more probable that the intima ruptures over a patch of mesaortitis, and in this way the aneurism starts. Stern[2] has collected a large number of cases from the literature. The aneurism may appear in a few days or not until many months have passed.

In a few rare cases aneurism of the aorta is of the *erosion* type. A tuberculous focus may involve the wall of the aorta, as in a case reported by Councilman. A bullet lodged in the wall without perforating it has been followed by aneurismal dilatation (Freyham).

Other causes may be mentioned. Mickle has called attention to the frequency of aneurism in the *insane.* This and the not very uncommon coexistence with *locomotor ataxia* is probably a syphilitic association. Lee Dickenson has described aneurism in connection with *hypoplasia of the aorta.* Both of his cases were in young adults with thin, narrow aortas, free from disease; one presented three aneurisms.

[1] *Deutsch. med. Wochenschrift,* 1905.
[2] *Ueber traumatische Entstehung Inneren krankheiten,* 1896.

Number, Form, and Size of Aneurism and Vessels Affected.—*Number.*—In the aorta the aneurism is usually single, but three, four, five, even a score or more, may be present. The multiple cup-shaped tumors in young men are always syphilitic. The mycotic aneurisms are often multiple; in one of the writer's cases there were five in the arch of the aorta. In the embolic form there may be a dozen or more in the smaller vessels. In certain individuals aneurism may occur in different vessels, simultaneously or in succession.

Form.—In the aorta there are two great types, the *cylindrical*, or *fusiform*, and the *sacculated*. In his study[1] Thoma calls attention to the physiological bulgings of the aorta: "The ascending aorta in the region of the semilunar valves presents an onion-shaped dilatation, the bulbus aortæ, in which are the sinuses of Valsalva. Immediately above the valves the lumen narrows distinctly, becomes circular, and then undergoes a second dilatation directed forward and to the right, known as the sinus quartus sive maximus Valsalvæ. This unilateral, spindle-shapted dilatation of the aorta also disappears again before the vessels of the neck are given off. After the origin of the left subclavian there follows a narrower portion of the lumen, the isthmus aortæ, after which the vessel again widens." As given in the plates illustrating the article, Thoma shows that in pathological states of the arch these physiological bulgings are followed; one or other or all of them may show dilatation, or the whole arch may be involved, forming a definite spindle. In other instances the arch is a huge, flabby sac scarcely retaining a semblance of its shape. Typical spindles are seen too in the arteries of the second and third dimensions, rarely in the smaller vessels. The cylindrical and fusiform are usually combined, as the dilatation tapers at either end. Sometimes the whole aorta or a large section of it is represented by an enlarged cylinder.

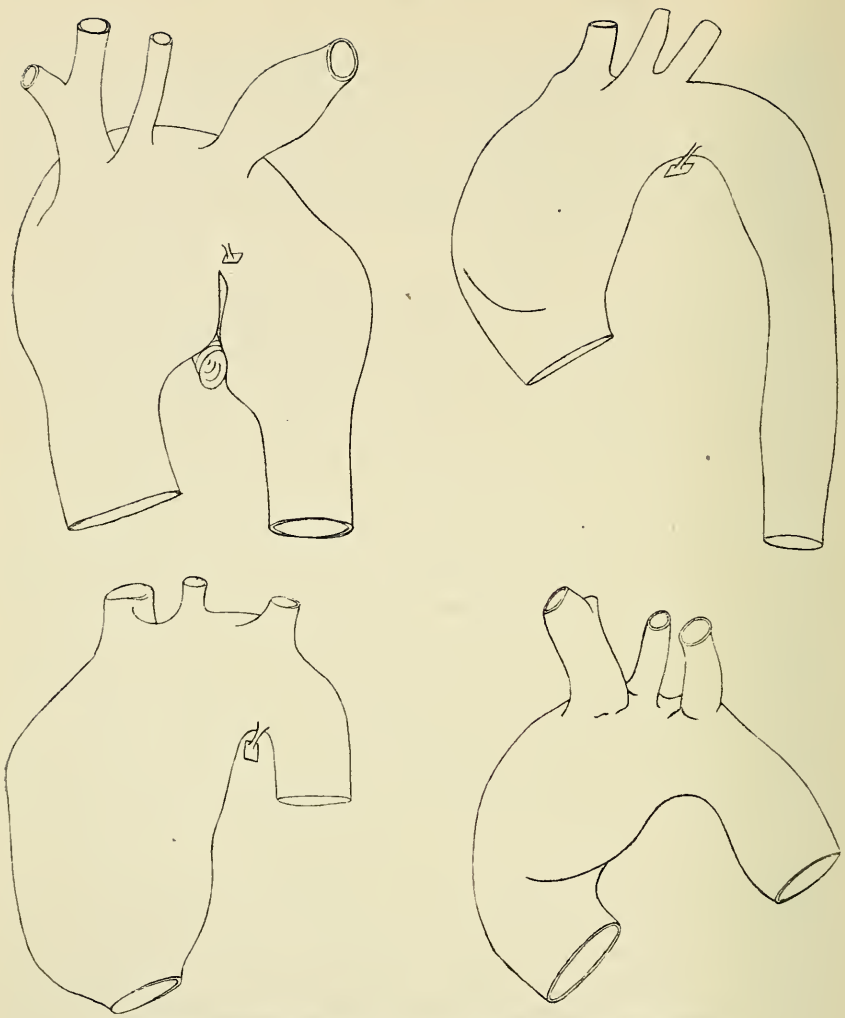
The *sacculated* form, in which there is a definite protrusion of one side of the wall, is the more common. The shape of the sac will depend on the extent of the area of the primary weakness of the wall; if large, the sac will be diffuse and crater-like; if small in relation to the aorta, it may have a small orifice, slit-like, oval, or round, leading into a circular pouch. Some sacs are flat, saucer-shaped, others cup-shaped, others pear-shaped, almost pedunculated, with a narrow neck. The saccular aneurism may arise on the wall of a diffuse dilatation, or a saucer-shaped sac may have two or three small ones upon it. Occasionally there is seen an aneurism of multilocular aspect, which has arisen from the excessive development of these secondary sacs.

In the small arteries, as of the brain and kidneys, these same types are seen—the saccular more often than the fusiform. The special forms of dissecting and arterio-venous aneurisms will be described later.

Size.—From a pin's head to the head of a child. There are almost microscopic tumors of the small arteries, while a sac connected with the aorta may fill one-half of the chest. When perforation of the chest wall occurs, or when there is a diffuse aneurism of the abdominal aorta, the size of an adult head may be reached, and with its contents the aneurism may weigh five or six pounds.

[1] Untersuchungen über Aneurysmen, *Virchows Archiv*, vol. cxi.

Fig. 43



Forms of dilatation in aneurism of the arch of the aorta. (After Thoma.)

Vessels Affected.—Crisp's statistics of 501 cases are the best:

Popliteal	137
Thoracic aorta	125
Femoral iliac	66
Abdominal aorta	59
Carotid	25
Subclavian	23
Innominate	20
Axillary	18
External iliac	9
Intracranial	7
Pulmonary artery	2
Common iliac	2
Gluteal iliac	2
Posterior tibial	2
Temporal	1
Ophthalmic	1
Suprascapular	1
Brachial	1

Life History of an Aneurism.—Against the incessant strain offered by the pumping of blood sixty to eighty times a minute, the artery is protected by the elastic and fibrous tissues of the media and adventitia. Weakened at one spot and yielding, it is then a struggle between the blood pressure and the remnants of the tube at the affected spot—an unequal struggle, as the sac gradually yields. But nature does not rest passive. Only in the very acute cases is no attempt seen to limit the mechanical progress of the disease. In nearly all aneurisms healing is attempted by two processes, with two tissues, the one mural and the other hemic, a new growth of connective tissue and fibrin formation.

(*a*) Connective-tissue healing of an aneurism, seen to perfection only in small forms, is an intimal affair; in large sacs the adventitia play the chief part. We owe to Thoma the first good account of this method of healing. Fig. 44, here reproduced, shows a small sac on a branch of the ophthalmic artery entirely obliterated, with a growth from the intima in such a way that the inner surface of the artery and of the sac are on a level. Although the same process may go on in the large vessels (and Thoma figures an example in the abdominal aorta), it is much less rare than in the small branches. In every aneurism still lined with intima this compensatory thickening is to be found. But under the influence of the blood pressure the sac, as a rule, grows at such a rate that the endarteritis cannot keep pace with it. In the common saccular aneurism the reparative process from the adventitia is much more important. There is active proliferation of the fibrous elements, and although it may yield and be thin at the point of greatest pressure, in the larger sacs there is found great thickening which is not always easy to differentiate from the surrounding connective tissue.

Fig. 44

Cross-section of the ophthalmic artery showing diffuse arteriosclerosis and healing of an aneurism by intimal thickening. (After Thoma.)

The *lining* of an aneurism may be the thickened intima (which is only the case in very small tumors), the media, in whole or in part, or, as the sac enlarges, the adventitia alone. Then comes a stage in the growth of the larger tumors in which part of the sac is no longer composed of an arterial coat, but is in direct connection with adjacent tissue, bone, lung, skin, or the structure of the mediastinum. In the big dilatation aneurism the intima may be everywhere unbroken, but thickened and roughened with calcareous plates and areas of atheromatous softening. In the saccular form the intima may be traced only to the orifice or for a short distance into the wall of the sac.

The second great element in the repair of an aneurism is *thrombosis,* the deposit of laminated fibrin in the sac. It does not occur in every case, even under conditions which look the most favorable. In a typical degree the deposition of fibrin is seen in the sacs with narrow necks, but it may be seen in the fusiform dilatation of any part of the aorta. In cutting across an aneurism in which this process has been going on, firm, hard, leathery sheetings of grayish-brown fibrin are seen, arranged in layers which may be peeled off like the flakes of an onion. In large sacs from 25 to 50 laminæ may be counted. The gradual formation of these is most interesting. One often finds on the lining membrane of a small-sized sac most remarkable deposits of platelets, usually ribbed like sand on the seashore or arranged in a tracery or network. The areas with the platelets show as grayish-white, soft thrombi, quite different in appearance to the reddish-brown ground substance on which they are deposited. Gradually the aneurism may become filled even to the mouth, and in this way permanent healing may be effected. At first the layers of fibrin are reddish brown in color, but in the very old sacs they are grayish white, and occasionally lime salts are deposited, so that the whole becomes a firm, calcareous mass.

Pressure Effects.—With the gradual growth of the sac remarkable effects of compression are seen. Passing anteriorly, an aneurism of the arch erodes the sternum, destroys the costal cartilages, fractures the ribs, which gradually become absorbed, and finally, there may be a hole in the front of the chest into which the two fists may be placed. Posteriorly, an aneurism of the descending thoracic aorta may perforate the chest wall and destroy four or five ribs, causing complete atrophy of the muscles in its course, and appear beneath the skin as a large flabby sac, as is very well shown in Fig. 49. Not less remarkable effects of erosion are seen in the spine, the bodies of three, four, or five of which may in large part be absorbed and the roughened bone forms part of the wall of the aneurism. A remarkable fact, noted by Morgagni, is that the intervertebral disks are not destroyed at the same rate as the bone, and may remain more or less intact while the bodies are deeply eroded. The exact method of this destruction of bone is much discussed. Some have ascribed it to a dissolving action of the blood, others believe it to be entirely mechanical, due to the pressure and shock of the systole. Cornil and Ranvier describe it as a rarefying osteitis, a low grade of inflammation by which the bone is gradually removed. Other effects of compression and the modes of perforation will be described later.

ANEURISM OF THE HEART.

1. **Aneurism of the Valves.**—Weakness of the tissue of the valve results from erosion, from myotic ulceration, or from softening of an atheromatous focus. There are acute and chronic forms. The acute valvular aneurism is seen most commonly on one of the aortic segments projecting from the ventricular side in globular form of the size of a pea or of a small nut. Sometimes it involves the entire valve. It may be

at the line of attachment, so that there is partial aneurism of the sinus of Valsalva as well. It may be the only lesion, although more frequently it is associated with destructive changes. In very many instances the aneurism is perforated. Two, three, or even four little sacs have been found. Involvement of the mitral segments is not so common—the anterior valve more frequently then the posterior. The chronic atheromatous aneurism is a very different affair. Following the softening of a subintimal focus, it is usually seen in sclerotic or partially calcified valves, and in the aortic more often than in the mitral segments. Thrombi may be deposited; in one instance they were firm and laminated.

2. **Mural Aneurism.**—Two forms may be recognized, the acute and the chronic.

Acute Aneurism.—Acute aneurism, an event in connection with ulcerative endocarditis of the heart wall, is seen most frequently on the left side in the upper portion of the septum near the aortic ring, but it may occur on the right ventricle, and even in the auricles. Perforation is apt to take place into the pericardium or one of the other cavities, or into one of the larger vessels. A variety of this is the dissecting aneurism of the heart, of which Vestberg[1] has collected 60 cases.

Chronic Aneurism.—This is an event in connection with fibrous myocarditis. It is not very uncommon, particularly the slighter forms. Strauch collected 55 cases which occurred in Berlin, chiefly at the Charité Hospital within ten years. There were 3 cases at the Johns Hopkins Hospital among 3000 postmortems. It is much more common in men than in women—64 out of 80 cases (Wickham Legg); 38 out of 55 cases (Strauch). The majority of the patients are above fifty years of age. A case has been reported in a boy of ten (Rosenstein).

Etiology.—The etiological factors are those of arteriosclerosis and chronic myocarditis. In Strauch's series 44 of the cases presented myocarditis alone without valve lesion. It is usually stated and it certainly has been the writer's experience, that the coronary arteries are involved or the anterior branch is calcified and narrowed; but Strauch's cases do not bear out this view, as only 15 showed involvement of the coronary arteries. He regards it as a special pathological change, a degeneration which is difficult to connect with any other heart lesion. Syphilis did not appear to be a factor in many cases. The left ventricle is affected in almost every instance, in all of Strauch's series, and in a large majority the apex region is involved, extending toward the septum. Usually single, there have been cases reported with two or even three aneurisms. In the most characteristic form there is a globular distension of the apex region of the heart, with perhaps slight thickening of the pericardium or a definite change in the appearance of the muscle. The tumor may be the size of the first, or even larger. From within thrombi are usually seen, attached to a sclerotic endocardium. On section of the wall of the sac the heart muscle may in great part be converted into fibrous tissue. The thrombi have been found calcified. As a rule, the sac is flat, in a few cases quite globular and communicating with the cavity

[1] *Nordiskt Med. Arkiv*, 1897.

of the ventricle by a narrow orifice. Cases have been described in which the sac has been larger than the heart itself.

Symptoms.—The symptoms are very obscure, and it is rarely possible to make a diagnosis. The cases are usually mistaken for chronic myocarditis, or the diagnosis is made of the associated valvular lesion. As the aneurism is at the apex and enlarges the left ventricle, the features of hypertrophy and dilatation are usually present. Symptoms of angina pectoris are not infrequent. Strauch has carefully analyzed the physical signs presented in a select group of his cases without throwing any very special light on the possibility of diagnosis.

DILATATION ANEURISMS

There are two important groups: (1) In one, seen chiefly in the aorta and larger branches, the artery has passively dilated, owing to disease of its walls; (2) in the other, seen most frequently in small branches, there is an active dilatation due to growth and enlargement of the vessel.

Dilatation Aneurism of the Aorta.—New interest has been attached to this form since the introduction of the *x*-rays in clinical diagnosis. Formerly it was overlooked to a great extent even in the best clinics. In witness of this may be mentioned the striking fact that of the long series of cases studied by Thoma[1] scarcely one had been recognized in the wards, though under the care of one of the most skilful clinicians in Europe.

Joseph Hodgson,[2] in 1815, described what he called "a preternatural, permanent enlargement of the cavity of an artery," and distinguished it clearly from ordinary aneurism. He recognized its association with disease of the coats of the vessel, and remarked that saccular aneurism could be engrafted upon it. The dilatation, which might be partial or complete, affected most frequently the ascending aorta. He very acutely observes that the symptoms suggest organic disease of the heart rather than aneurism. Since Hodgson's date this form has been well recognized anatomically, but it has not received enough consideration clinically, and yet it is one of the most common forms in the aorta. Scarpa, too, in his great treatise, while recognizing dilatation of the whole tube of the aorta, regarded it as essentially different from aneurism, although he says the two may be sometimes found together. Morgagni made a clear division between two kinds, one in which the tumor occupies the whole circumference of the arterial tube, the other in which the aneurism only affects one side of the artery. Primarily a disease of the media causing weakening, there are usually associated changes in the adventitia and extensive alterations in the intima. Among the forms recognized by Thoma are: (1) the multiple spindle-shaped aneurism; (2) the single fusiform aneurism; (3) the saccular engrafted or spindle form; and (4) the tent-shaped or sphenoid, a special form in connection with the upper part of the thoracic aorta, which he thinks, results from abnormal tension at this point just where the upper inter-

[1] *Virchows Archiv*, vol. cxi.

[2] *A Treatise on the Diseases of Arteries and Veins*, London, 1815.

costal arteries are given off. He lays great stress on the involvement of the adventitia, and with the periarteritis he would associate the attacks of pain so common in this condition. While, as a rule, this form is met with in old persons and is associated with extensive endarteritis deformans, one meets with a few cases in which the arch is considerably dilatated with a smooth or not much involved intima.

Associated quite frequently with this dilatation of the arch is insufficiency of the aortic valves, due either to a sclerosis and shortening of the segments or to dilatation of the ring itself. It is to this combination particularly that the French give the name, *Maladie de Hodgson,* but in the original description of this author it does not seem that he refers to the associated disease of the valve.

In young men with syphilis the process may be limited to the arch, which in any case is most common, but it may involve the entire aorta. In nearly all cases there is extensive endarteritis deformans with calcified laminæ and atheromatous erosions. The dilatations may be onion-shaped or spindle-formed. They may be multiple. Sometimes on the wall of the spindle-formed dilatation there are small saccular aneurisms. Thoma's admirable paper gives outline figures of the various forms, all of which owe their origin directly to the action of blood pressure on the diseased vessel wall.

The dilatation aneurism is very common, particularly in old people, and is often found accidentally. Only when of a very large size does thrombus formation take place in it. There is a remarkable specimen in the McGill Museum presented by R. L. Macdonell, in which the descending thoracic and abdominal aorta, and the iliacs were greatly dilatated. The abdominal aorta forms a fusiform aneurism, which is filled with a densely laminated thrombus. In other instances the whole aorta is dilated, or the arch may be double or treble the normal size and without thrombi on the roughened intima.

Symptoms.—There are three groups of cases: (*a*) Latent: The condition is met with accidentally in medicolegal work or in the postmortem-rooms of almshouses and infirmaries, particularly among old people. The dilatation may reach an extreme grade without any special symptoms. (*b*) With the picture of *angina pectoris:* In the syphilitic aortitis in men under forty years there may be no dilatation of the arch, but in the senile dilatation of the arch angina is a common, sometimes the only, symptom. The attacks of pain may recur at intervals for several years without any sign of cardiac insufficiency. (*c*) In a third group the features are those of organic disease of the heart, usually of aortic insufficiency, characterized by attacks of vertigo, dyspnœa, cough, and the usual symptoms of cardiac failure, which may be present for weeks or months before the end comes. Hodgson recognized the fact that the clinical features of the condition were very often those of valvular disease. The incompetency of the valves may be due to the distension of the aortic ring.

Physical Signs.—*Inspection* may show a diffuse impulse over the manubrium, but in old persons with rigid chest walls and a calcified aorta there may be an extreme degree of dilatation without a visible

impulse. The top of the aorta may reach to the sternal notch, and the innominate artery is elevated; but it is to be remembered that the throbbing in this situation is much more frequently due to the right carotid as it leaves the innominate, or to the innominate itself, than to the arch. The right subclavian is often visible above the clavicle. An impulse may be seen on either side of the sternum in the second and third interspaces. Palpation may detect a systolic thrill, rough and harsh in cases of calcification on the intima, sometimes diastolic when the valves are insufficient. With one hand on the manubrium, the other on the spine, pressure may detect a deep pulsation. In the sternal notch the forcible throbbing of the dilated aorta may be felt. Tracheal tugging may be present. *Percussion* gives dulness over the manubrium and sometimes in the adjoining first and second interspaces, varying with the extent of the dilatation.

Auscultation.—A systolic murmur is heard, often of great intensity, and propagated into the vessels of the neck. There is nothing distinctive in it, nor does it differ from the bruit so often heard over the aorta in old persons with sclerosis. A diastolic murmur, if present, is more important, as it may be heard up the sternum, often quite loudly, and is even propagated into the vessels of the neck. The aortic second sound may be of a remarkably metallic quality and loudly heard up the sternum. The fluoroscope shows a pulsating shadow, larger and higher in position than the normal aorta, and which does not disappear in diastole.

Active Dilatation Aneurism. Cirsoid Aneurism.—No structures retain their powers of growth in greater degree than the arteries. Many physiological conditions demand the retention of this property; for example, the arteries of the uterus at term are four or five times as large as in the unimpregnated state. In tumors, in the enlarged spleen, in the proximal branches after ligation of a main trunk, the arteries not only increase in size, but there is an active development showing to what an extraordinary degree these structures possess the capacity for new growth. With this power it is not surprising that we meet with instances in which spontaneously, at any rate from unknown causes, arteries enlarge. The condition is known as aneurism by anastomosis, racemose aneurism, or, more commonly, *cirsoid aneurism*. The arteries of the fourth and fifth dimensions are the most frequently involved vessels, for example, of the size of the radial and its immediate branches, or of the temporal arteries. The dilatation may be confined almost entirely to the arteries themselves. In other instances the veins are involved, and the smaller vessels, even the capillaries, may be implicated, so that the structures form a diffuse angioma. The situations most frequently involved are the head and the hands, but the arteries of any part of the body may be affected and the aneurism may be single or multiple.

There are three important exciting causes. The dilatation may arise in small birthmarks or little angiomas, particularly those about the ear and forehead. With a gradual increase in size, the arteries become convoluted and throb forcibly. In a second group of cases the aneurism

follows directly upon an injury, in one instance a burn on the hand, another, a blow on the head with a club, and the third, a slap on the face. And thirdly, in an interesting series of cases the tumor arises as a sequence or during an attack of fever. Two such cases are reported by Bazy.[1] At the Johns Hopkins Hospital we had a patient in whom multiple cirsoid aneurisms were present; following an attack of typhoid fever there was a decided increase in the size of the vessels. Reverdin suggests that all sorts of infectious arteritis may be the starting point of the aneurismal dilatation.

Symptoms.—Small tumors may cause no inconvenience. There may be slight swelling of the skin over the bunch of dilated arteries, and when the hand is placed upon it the individual vessels are felt to be convoluted and dilated; the pulsation is forcible, there is usually a thrill to be felt, and with a stethoscope a loud whirring murmur is heard. If the arteries alone are dilated, this may be systolic and single. In other cases where there are large venous anastomoses, the murmur is more or less continuous with systolic intensification. In other cases, particularly about the ears and temporal region, the skin itself is involved. There is marked swelling with a bluish tint, the dilated arteries are visible, telangiectases are present in the skin, or, if the whole process has started from a small birthmark or a nevus, the entire tumor may present the character of an angioma. The side of the face and head may be involved, and exophthalmos be present on the affected side. Huge tumors of this kind are reported, and they have at times increased with the rapidity of a new growth. Arising spontaneously, they have been known to disappear in the same way. A remarkable case is reported by Fernell.[2] A man aged twenty years, had a large pulsating tumor above the right clavicle which had lasted many years and which involved all the branches of the thyroid axis except the inferior thyroid; the transversalis coli and suprascapular could easily be made out, greatly enlarged and tortuous. During an attack of measles, in which the temperature rose to 106.5°, the tumor looked very red and angry, and pulsated very strongly, as if about to rupture. A compress was applied and veratrum viride, ergot, and iron were given. Following the attack of measles the tumor began to subside, gradually the pulsation and thrill disappeared, and it shrank to a mass of hard connective tissue which could be rolled about.

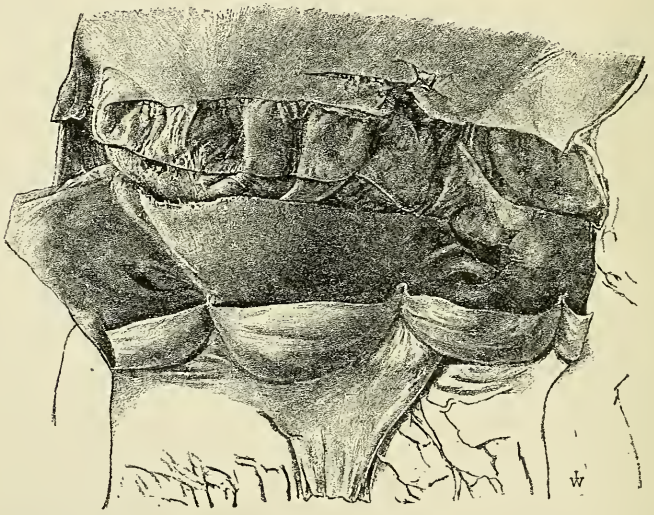
DISSECTING ANEURISM.

Splits and Fissures of Intima. Rupture of Aorta. Healed Dissecting Aneurism.—1. **Splits and Fissures of the Intima with Healing.**—In the artificial production of aneurism, there is sometimes found over a patch of mesarteritis a small slit or fissure of the intima, cleanly cut as if with a knife, evidently due to rupture. Behind this there may be a small pouch-like distension of the media and adventitia, or a little dissecting aneurism. Precisely the same thing happens in man, and there may be spontaneous rupture of the intima in the form of a small

[1] *Gaz. des Hôpitaux*, 1889, p. 1363.
[2] *St. Louis Courier of Medicine*, 1887.

slit one-fourth to one-half inch in length, or the entire circumference of the intima of the aorta may be cut through as if with a knife. A most remarkable circumstance is that these lesions may heal completely, leaving scars of the most extraordinary character. The cases are not very numerous in the literature. Von Recklinghausen described the case of a woman who died postpartum of a rupture two inches long of the inner coat of the ascending aorta. In the descending aorta an inch below the duct there was a split of the intima completely encircling the tube which was entirely healed. Zahn reports a case of a woman, aged thirty-seven years, dead of pneumonia and an aneurism of the aorta. Sixty millimeters from the ring there were healed splits in the intima and the media. The latter coat was not quite cut through, and this he thinks was the cause why a descending aneurism was not formed.

Fig. 45



Illustrating a complete transverse split of the intima of the aorta. (After v. Schrötter.)

By far the most important study in the healing of those splits and tears is in the well-known paper by Rokitansky.[1] He had not at that time seen a case of complete healing of a dissecting aortic aneurism, but he well remarks that the healing of the tears of the inner coat of the aorta, which he had figured, are not less remarkable. He reports five cases of healed splits of the intima. In Deland's case, the heart of which was dissected by the writer, in the first attack the intima of the aorta had split in the entire circumference and there was a fibrous cicatricial ring just above the valves. There was no pouching, and the margins of the intima were rounded and smooth. It looked an old and healed lesion. Farther up the arch was the fresh knife-like split of the intima and rupture into the pericardium.

[1] *Denkschriften der Kaiserblichen Akademie der Wissenschaften*, Band iv, Wien, 1850.

2. **Spontaneous Rupture of the Aorta.**—Traumatic rupture is not uncommon in medico-legal work. Spontaneous rupture is rare, but it may occur in a vessel apparently healthy, either as a result of sudden strain or sometimes without any effort. It may occur during confinement or in sudden muscular effort. It has occurred in a healthy boy aged thirteen following prolonged exertion. In the majority of the cases it is an intrapericardial rupture. The intima may be smooth and the lesion is usually sharp and well defined, as if cut with a knife. The rupture in the external coat is rarely directly opposite that in the intima, so that there is usually some evidence of dissecting aneurism. The cases present very characteristic clinical features, the symptoms occurring in two stages.

The case reported by Linn[1] is a good illustration: a woman, aged twenty-nine years (who had twice miscarried), in her third pregnancy, within fourteen days of term and without any special effort, complained of pain in the side and cardiac oppression. During labor, just after a pain, she started up in bed with an agonizing pain in her heart, and said she was dying. She became cold and pale and pulseless. She revived for a few minutes and was delivered in about two hours of a dead child. She remained cold and faint, with a small, quick pulse, and Linn thought the heart was ruptured. She improved gradually and seemed to be doing very well until the fourteenth day after delivery, when she again complained of a sudden pain in the chest, and she died in a few minutes. A very good illustration accompanying the paper shows an aortitis with rupture into the pericardium. In a woman at this time of life, who had had miscarriage and such a condition of the aorta, the trouble was no doubt due to syphilis. Of the two clinical periods, one corresponds to the rupture of the intima, with which is associated the severe pain and collapse, from which the patient gradually recovers. Then in the course of three or four days external rupture takes place with sudden death. In some instances the interval may be for fourteen days.

3. **Dissecting Aneurism.**—In ordinary practice and in the work of a general hospital, dissecting aneurism is not very common. There were only two cases in sixteen years at the Johns Hopkins Hospital, where aneurism may be said to be exceptionally frequent. And yet it is a common event, particularly in medicolegal work. A most interesting collection is in Boston, where, in the Warren Pathological Museum, there are twenty cases of dissecting aneurism and rupture of the aorta, most of them collected by the late J. B. S. Jackson. The writer is indebted to Joseph Pratt for getting the details about the cases. Apart from the traumatic instances, there are two groups of cases: the first, occurring in comparatively young persons, results from a rupture of the intima over the middle and external coats, weakened by syphilitic or some other form of aortitis. In the second group, occurring in elderly or very old people, there is extensive endarteritis deformans, and the rupture takes place at the edge of an atheromatous erosion, or an atheromatous intima may be split during a sudden exertion. The most frequent site is the arch and in its ascending portion. But the rupture may occur in any part of the aorta or in one of its main branches.

[1] *Medical Records and Researches*, London, 1768.

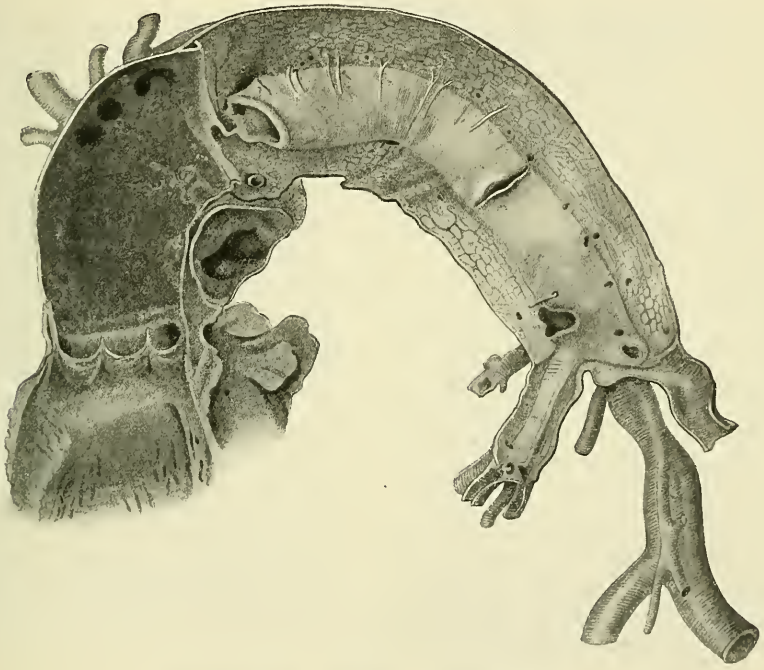
One of the early cases in which it was recognized was that of George II, who died suddenly of a rupture of the right ventricle. There was in addition in the trunk of the aorta a transverse fissure an inch and a half in length, through which blood had recently passed under its external coat and formed an elevated ecchymosis. As a rule, the blood infiltrates between the layers of the media, sometimes between the media and the adventitia. The extent of the splitting varies from a small area, such as that reported by Nicholls in the case of George II, to a complete separation of the coats of the entire aorta. There are instances on record in which the blood has passed down the crural arteries far into the vessels of the legs. Rupture may take place externally, which is very frequent, into the pericardium, for example, or internally in one or more places into the lumen of the aorta itself. The extent of the circumference of the vessel involved varies very greatly. In some instances only a small section is involved, in others there is a separation of a large part of the circumference, and the vessels may be torn across, although more frequently they are spared. In some cases the intracostal arteries, the cœliac axis, the renal vessels, and superior mesenteric have been torn across. A great majority of the cases of dissecting aneurism prove fatal. The symptoms are those already mentioned in connection with spontaneous rupture of the aorta, a sudden sharp pain, collapse, and death follows in from two to fourteen days from bursting of the aneurism. But in a few cases recovery takes place with an illustration of the most remarkable reparative processes seen in the human body, the formation of a healed dissecting aneurism.

4. **Healed Aneurism.**—Shekelton,[1] a Dublin surgeon, first reported cases of this kind, one of the abdominal aorta and the other of the left common iliac. In his first case so similar was the structure to that of the artery that he was inclined to regard it as an anatomical anomaly, but in the second case the doubt was cleared. Henderson, of Edinburgh, in 1843, reported a remarkable case,[2] in which from just behind the origin of the left subclavian the entire aorta consisted of two tubes. The outer canal communicated with the inner through an orifice into the left common iliac artery. The outer tube did not extend around the entire circumference. Both Shekelton and Henderson appreciated the true character of this remarkable condition. But Hope, in his well-known work on *Diseases of the Heart*, in referring to a case, thought that it was a congenital anomaly, a double aorta. Indeed, when one sees a specimen it is not surprising that this mistake has been made. The best accounts of the condition are given by Böstrom,[3] and by Adami,[4] who has been able to collect altogether 39 cases, among which women were almost as numerous as men. An interesting point is the fact that in a majority of the cases there was no advanced disease of the aorta. This is as we should expect, since, as mentioned in connection with spontaneous rupture, it is due to weakening of the media, and the intima

[1] *Dublin Hospital Reports and Communications*, vol. iii, 1822.
[2] *London and Edinburgh Monthly Journal of Medical Science*, vol. iii, 1843.
[3] *Deutsches Archiv f. klin. Med.*, Band xlii.
[4] *Montreal Medical Journal*, 1896, vol. xxiv, p. 945.

may show little or no atheroma. The site of the primary rupture was in the ascending aorta in 13 cases, below the origin of the left subclavian in 12 cases, the lower part of the thoracic aorta in 5 cases, in the abdominal aorta and iliac artery 1 case each. As already mentioned, the outer tube may extend the entire length of the aorta and occupy a variable section of the circumference. The branches of the aorta very frequently take origin from the outer sac. A feature which perhaps attracts most attention and has no doubt led to the belief that in these cases a congenital anomaly exists, is the smooth, natural appearance of the outer tube. Rindfleisch showed that a growth of endothelium took place, with the formation, in part at least, of a new intima.

Fig. 46



Healed dissecting aneurism. (After Böstrom.)

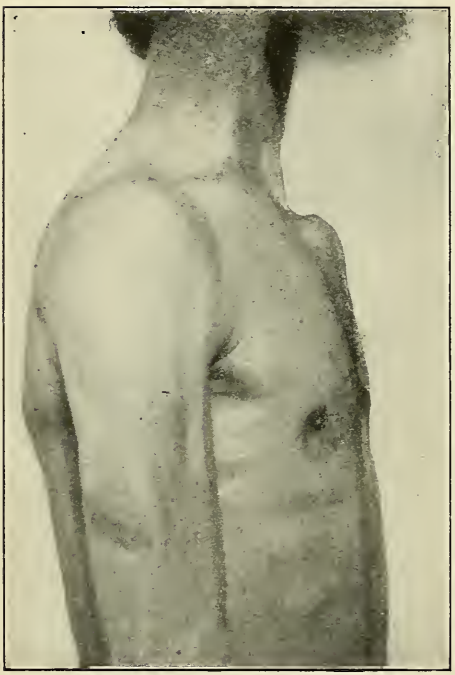
The duration extends over many years. When a student in Toronto, the writer frequently visited the gaol with his old friend and teacher, Professor Richardson, and at intervals they saw there a soldier who had been discharged from the British army soon after the Crimean War for aneurism. He seemed a very healthy man, and there was no evidence of any existing tumor. He died in 1886, and J. E. Graham, who made the postmortem and who reported the case, kindly sent the specimen to me for dissection. There was a small healed aneurism at the third portion of the arch, and from the margin of this sac, just beyond the left subclavian, the aorta formed a double tube. There was little question that this had lasted for more than thirty years from the time of his discharge from the army with symptoms of aneurism.

SACCULATED ANEURISM

As the great majority of cases of sacculated aneurism in medical practice affect the aorta, we shall deal with the disease as it is met with in this vessel. For convenience of description we may divide the aorta into three parts—the arch, the descending and the abdominal portions:

Aneurism of the Arch of the Aorta.—As already mentioned, this part of the vessel may be uniformly dilated, but it is much more common to have one or other portion involved in a saccular aneurism situated in a sinus of Valsalva, the ascending or the transverse portion of the arch.

FIG. 47



Aneurism of the thoracic aorta.

FIG. 48

Aneurism of the subclavian artery.

Aneurism of a Sinus of Valsalva.—Aneurism of a sinus of Valsalva is a common and important variety, met with particularly in syphilitic subjects and in comparatively young men. There may be a pouching of all three sinuses, but more commonly one only is involved. The orifice of a coronary artery may be given off from the sac, and the first part of the vessel may itself be dilated. The aortic ring may become involved and the adjacent semilunar valve may be rendered incompetent. The aneurism may perforate one or other auricle from the right posterior sinus, or into the pulmonary artery or the right ventricle from the left posterior sinus, or from the anterior; or the sac may pass beneath the ring and perforate into the left ventricle itself. By far the most common

perforation is into the pericardium; or rupture may take place into the superior vena cava. There are cases in which the aneurism seems to be given off directly at the aortic ring and involve as much of the ventricle as of the sinus.

Aneurism of this portion of the arch has very definite features: (*a*) It is not detected in the wards, but is seen in the dead-house, particularly in connection with medicolegal work. (*b*) It is very often latent, death occurring from perforation before there have been any symptoms. (*c*) It is frequently syphilitic. (*d*) Angina pectoris may be an early feature. (*e*) Aortic insufficiency is a common accompaniment.

Aneurism of the Ascending Arch.—Perhaps the most common situation for the saccular tumor is from the convexity of the aorta, an inch or so above the valve. The tumor grows freely to the right, displacing the vena cava and the lung, and some of the largest sacs met with originate in this situation. Anteriorly, it appears to the right of the sternum, in the second and third interspaces, and may gradually erode the bone and cartilage, and, passing upward, lifts the sternoclavicular joint and appears as a large, external tumor. The sac may perforate into the pericardium, the right auricle, the superior vena cava, the lung, the right bronchus, or passing backward, erode the spine.

Aneurism of the Transverse Arch.—Owing to the very small space between the spine and the sternum, the tumor here is restricted in its growth, and is likely to cause early and severe symptoms from pressure, particularly upon the windpipe. The left recurrent laryngeal is involved, and changes in the voice, attacks of dyspnœa, and painful dysphagia are common. Small tumors may cause the most intense symptoms without, indeed, any physical signs. Although in this situation the sac, as a rule, does not grow to such a size, yet there are instances in which the extension laterally has been enormous, producing some of the largest and most chronic types of aneurism. Growth backward may involve the spine, producing agonizing pain.

Physical Signs.—*Inspection.*—The well-known dictum may be taken as a text: "More mistakes are made by not looking than not knowing." A majority of aneurisms of the thoracic aorta present suggestive features to the eye, but the inspection must be made with care. A good light, good eyes, a bare chest, and system are indispensable. There are dark consulting rooms in which it would be impossible to see the slight throbbing to the right of the sternum or the general diffuse heave of the manubrium. Even in a good light one may look directly at a pulsation and not see it. The point of view is everything, and it is best to examine the patient on a revolving stool, which can be turned easily so as to get the effect of the light falling at different angles. Good eyes are the physician's best tools, but it is not merely acuteness of vision, though this is important, but it is the educated, seeing eye, which is only to be had by careful training.

"Strip to the buff" is the rule. If the shirt and undershirt are tucked up to save time, the all-important area above the level of the second rib may be covered. More than once it has happened in the writer's experience to have the sought-for diagnosis stare at the astonished doctor

from the first or second interspace or the supraclavicular region. System is most important: apex region first, then along the sternal margins, the sternal notch, the supraclavicular fossæ, the state of the neck, the superficial veins, the skin, the larynx, the face, eyes, pupils, the epigastric region, all these in quick succession in a preliminary survey, and then anything which attracts attention may be looked at in more detail. Turn the patient and examine the back, particularly the interscapular areas. If not done in order as a routine, the chances are that it will be forgotten as the interest increases in other parts of the examination, and perhaps the diagnosis may be missed altogether. Certain cases make an enduring impression on one. In 1888 the writer saw, at the Girard House in Philadelphia, a man with orthopnœa, a greatly dilated heart with an unusual widespread impulse in the lower sternum and adjacent parts. There was a loud, diastolic murmur, and the whole trouble had been attributed to aortic insufficiency. But there were very puzzling features in the case, which need not here be discussed. After finishing the examination in front the patient's back was turned to the light, when the diagnosis was instantly seen in the form of a prominent pulsating tumor in the left interscapular region, which had been overlooked. The writer on several occasions has missed the diagnosis by carelessness in the routine examination. In a patient named McKinley, very well known to a succession of classes at the Johns Hopkins Hospital, when first seen at the out-patient class, we were so interested in the physical signs in the front of the chest, which were those of a very obscure heart trouble, that we forgot to look at his back. In the ward the House Physician made the diagnosis for us on inspection of the patient's back. There is no disease more conducive to clinical humility than aneurism of the aorta. Mistakes occur with the most careful and the most skilful. Sometimes the diagnosis is beyond our art; more often it is not made because of the carelessness that so easily besets us in our work. The confession of the great Pirogoff always seems to me most touching: "There are in everyone's practice moments in which his vision is holden, so that even an experienced man cannot see what is nevertheless perfectly clear, at least I have noticed this in my own case. An overweaning self-confidence and preconceived opinion, rarely a weariness, are the causes of these astonishing mistakes."

Face.—The subjects of aneurism are generally robust, vigorous-looking young or middle-aged men, with what is sometimes called the cardiovascular facies. Marked suffusion of the face is common when the aneurismal sac presses on the veins near the heart. The conjunctivæ may be dusky and infiltrated, and occasionally there is cyanosis. These features of venous compression are not, however, so common in aneurism as in tumor. Occasionally the congestion of the veins may be unilateral.

Inspection of the face gives us the interesting features supposed to be associated with pressure on the cervical sympathetic. Of these, inequality of pupils, *anisocoria*, is the most common. This is present in a very considerable number of cases, and may be due to three causes: (1) When the cord of the sympathetic in the neck is irritated there is contraction of the pupil on the affected side; when there is complete

paralysis there is dilatation. Associated phenomena of sympathetic irritation are flushing, unilateral sweating, and drooping of the eyelid. (2) Cecil Wall and Ainley Walker have brought forward evidence to show that this anisocoria is due more often to local vascular conditions. The size of the pupil is influenced very largely by the state of turgescence of the vessels. With low blood pressure, large pupils, with a high pressure contracted pupils, are associated; and these authors think that the anisocoria in aneurism is associated with unilateral change in the blood pressure. In 26 consecutive cases of inequality of the pupils in thoracic aneurism they found that there was nearly always a relation between the state of the pupils and the arteries. Where the temporals or radials were small the pupil was large. Experimentally, too, they found that obstruction of carotid vessels in the neck was always associated with a large pupil. In one case of aneurism at the root of the neck on the right side, in which the pupils were equal, distal ligature of the common carotid was followed by enlargement of the right pupil, and an operation on the carotid is reported in which this same sequence followed. In the majority of individuals, pressure on the carotid on one side is followed by enlargement of the pupil. This study gives a very rational explanation of the phenomenon, and removes a very serious difficulty, namely, that very often pupil changes are found when anatomically the aneurism has no connection whatever with the sympathetic. (3) In a certain number of cases the inequality of the pupils is a parasyphilitic manifestation associated with the Argyll-Robertson phenomenon and absent knee-jerks.

Inspection of the neck may show great engorgement of the face on one or both sides, absence of the carotid pulsation on one side, sometimes enormous distension of the right jugular sinus, and in the aneurism of the arch or of the innominate arch together, pulsation of the tumor itself is visible just above the sternum or the sternoclavicular joint. An interesting feature sometimes seen is the visible *tracheal tugging*, a systolic retraction of the box of the larynx, and of the tissues of the root of the neck along the line of the windpipe which may show a lateral deviation.

Arm and Hand.—Sometimes there is swelling of both upper extremities. Particularly is this the case in the aneurism of the ascending aorta, which had grown to the right and compressed the superior vena cava. Much more commonly the arm on one side is congested with enlarged veins, less commonly cyanosis. Pallor and sweating may be present in one arm only. A very interesting feature is the unilateral clubbing of the fingers in thoracic aneurism, of which the writer has seen two cases, one on the right side and one on the left. It is associated with peripheral stasis. Groebel, of Nauheim, has reported several cases.

Skin of Chest.—Distension of the veins over the shoulder and pectoral region is common. A network of distended veins may be marked on the right side above the third rib. Very great enlargement of the mammary veins is not so often seen in aneurism as in tumor compressing the superior vena cava. The whole front of the chest may be occupied by large plexus of vessels communicating with the epigastric veins and

all the well-known features of obstruction to the blood entering the auricle from above.

Pulsation.—Three sorts of pulsation may be seen in the chest: (*a*) A general shock, such as is present with violent throbbing of the heart, of an aneurism, or of a pulsating aorta. In great hypertrophy of the heart and dilatation of the vessels with marked anemia, the front of the chest is lifted and jarred with each impulse, often the subclavians throb, and there is a pulsation in the suprasternal notch. Even without organic disease of the heart, as, for example, in cases of Graves' disease, neurasthenia, and severe anemia, this diffuse throbbing, particularly when associated with marked pulsation of the subclavians, may lead to the diagnosis of aneurism. The shock may be so pronounced as to jar the bed.

(*b*) A diffuse impulse localized over certain parts of the chest and quite different from the general thoracic shock. Usually limited to one side of the chest, to the right mammary or subclavicular regions, it may occur, as is well known, with pleural effusion, gaseous or liquid. There are remarkable instances in which this diffuse pulsation of one side of the chest has occurred without any very obvious cause. This throbbing may occur in anemia and be most deceptive, as in the case reported by A. R. Edwards, in which over the lower left chest there was a diffuse pulsation extending horizontally from the angle of the left scapula into Traube's space and the epigastrium—"the pulsation was vigorous and distinctly expansile to both the eye and the hand." A systolic bruit was heard over it. Naturally the case was regarded as one of aneurism of the thoracic aorta. The postmortem showed moderate arteriosclerosis of the aorta, but no aneurism. Lafleur reported a very similar case with pulsation in the same region, and in addition paralysis of the left vocal cord. And lastly, in chronic *mediastinitis* there may be a most deceptive pulsation simulating that of aneurism. In 1902 there was under the care of the writer for some months, a patient aged fifty-nine years, who had increasing dyspnœa, cough, and some pain in the chest; the fluoroscope showed an indefinite shadow to the left of the sternum. The voice was a little cracked, the arteries were thickened, and in the second right interspace extending toward the axilla was seen a diffuse impulse, very indefinite, when the breath was held. With other symptoms and a slight tracheal tugging, naturally a diagnosis of aneurism was made. W. T. Howard, of Cleveland, who made the postmortem, found a remarkable condition of chronic mediastinitis.

(*c*) *The punctate, heaving, true aneurismal impulse,* which is of a totally different character, localized, and when of any extent visibly expansile. It is first of all most important to recognize the regions in which the cardiovascular impulses may be visible. The apex beat in the fifth interspace and an impulse of the right ventricle in the left costoxiphoid angle are seen over the hearts of thin-chested, healthy persons. Other impulses which must not be mistaken for aneurism are the following: (1) The throbbing of the conus arteriosus in the second left interspace—very common in young persons and in thin

chests, and seen particularly well during expiration. (2) Pulsation of the heart in the second, third, and fourth interspaces, extending as far as the nipple line in cases of sclerosis and retraction, from any cause, of the upper lobe of the left lung. (3) Heart pulsation in the second, third, and fourth right interspaces in connection with similar conditions of the right apex. (4) Effusion in either side of the chest may so dislocate the heart that there is a marked impulse at or outside the nipple line on either side. (5) Throbbing subclavians seen in the outer half of the infraclavicular regions, usually bilateral; this is met with in thin-chested persons, in neurasthenia, in early tuberculosis, and in anemia. Sometimes it is unilateral, and when accompanied with a thrill and murmur it may form a mimic or phantom aneurism. Samuel West[1] has reported 8 cases of this kind. (6) In the back part of the chest visible pulsation is nearly always aneurismal; but occasionally, in Broadbent's sign the tugging may be so limited and localized in one interspace that it simulates pulsation, but palpation corrects this.

Palpation.—Over a blood tumor connected with the aorta and close to the heart, three things may be felt: (1) *The aneurismal impulse:* To appreciate its character one must understand that this is identical with the cardiac impulse, and to learn to recognize it one should practise carefully the palpation of an actively beating apex. The remarkable vigor and intensity, the impossibility of resisting it, the closeness under the fingers with the definite expansile quality, are its important features. These are only appreciated when the aneurism reaches the surface, but even when the sac itself cannot be palpated there may be communicated to the chest wall a forcible heave which is entirely different in sensation from the ordinary shock. In the deep-seated tumor beneath the manubrium this may sometimes be appreciated best by bimanual palpation—one hand upon the spine and the other forcibly compressing the sternum. The communicated shock or jar which is felt over the chest in a case of hypertrophied heart or a throbbing aorta is diffuse, without localization, without any punctate, heaving quality and without that sense of forcible expansion directly beneath the fingers which is so characteristic of the cardiac and the aneurismal beating. (2) Over the aneurismal sac near the heart may be felt the shock of either a thudding first sound or, what is much more common, the sharp flap of the second sound. The latter is of great diagnostic importance, and may sometimes be felt by the slightest application of the finger to the sac as a snapping, short shock. (3) *Thrill:* A marked vibratory thrill may be felt, usually systolic in character, much more rarely diastolic and not often double. Thrill is not a special feature of aneurism of the thoracic aorta, and a great majority of cases are without it. It is relatively more common in aneurism of the abdominal aorta. A diastolic thrill is exceedingly rare.

Tracheal Tugging.—When the sac is adherent to the windpipe, with each systole the larynx may be slightly drawn down, and if the finger be placed upon it, or if the windpipe is stretched, a slight tug may be

[1] *St. Bartholomew's Hospital Reports*, 1880, vol. xvi, p. 119.

felt. This very valuable sign, first described by Sergeant-Major Oliver, is present in a large proportion of all cases of aneurism of the arch when it is in contact with the windpipe. Occasionally it is present in great dilatation of the aorta and in tumors. It may be visible as well as palpable.

Inequality of the radial and carotid pulses is common. Usually the radial pulse on the one side may be slightly retarded or very much smaller. The carotid may be extremely feeble or obliterated, an event less common in this vessel than in the radial. The right pulse is more frequently smaller than the left. The inequality is most commonly due to involvement of the innominate in the sac with narrowing of its orifice. On the left side the subclavian, with or without the carotid, may be involved in the sac. Either subclavian may be compressed outside the sac. The radial may be smaller on the side opposite to that in which the sac is prominent. Thus a small radial on the left side with a projecting sac from the ascending aorta on the right side may be due to an atheromatous narrowing of the orifice of the left subclavian, or there may be a small secondary aneurism.

It was Harvey, I believe, who first noted the change of pulse in aneurism. In Chapter III of the *de Motu Cordis* he describes the following case: "A certain person was affected with a large pulsating tumor on the right side of the neck, called an aneurism, just at that part where the artery descends into the axilla, produced by an erosion of the artery itself, and daily increasing in size; this tumor was visibly distended as it received the charge of blood brought to it by the artery with each stroke of the heart; the connection of parts was obvious when the body of the patient came to be opened after his death. The pulse in the corresponding arm was small in consequence of the greater portion of the blood being diverted into the tumor and so intercepted."

The pulse may be imperceptible at the wrist and just felt in the brachial, or a very feeble impulse may be seen or obtained by the sphygmograph when nothing is felt by the finger. There are cases in which no pulsation is felt in any of the arteries of the head or of the upper extremities, generally instances of large aneurism of the transverse arch. It is much more rare to meet with obliteration of the pulse in the abdominal aorta or in the femorals. The writer reported one instance in which this interesting condition was present. Absence of the pulsation in a vessel does not necessarily mean that the orifice at the main trunk is obliterated. Feebleness of the pulse on one side may be due, as Harvey suggests, to the diversion into the tumor of the greater portion of the blood, and in the case of a very large sac the force of the cardiac systole may be entirely absorbed and an intermittent converted into a continuous stream.

Blood Pressure.—This may show variation in the two radials. O. K. Williamson has made a very careful study of this condition in 30 cases and finds that while the arterial blood pressure in aneurism is either normal or slightly above normal, in a majority of cases of thoracic aneurism there is a marked difference in the blood pressure in the two arms, and when this is greater than 20 mm. it is a point in favor of aneurism.

Percussion.—When the aneurism reaches the chest wall impairment of resonance shading to flatness is a common physical sign, detected most commonly to the right of the sternum, upon the manubrium, to the left of the sternum in the subclavian and mammary areas, and in the left interscapular region behind. When the sac is closely surrounded by lung the impairment of resonance may be very slight and only brought out on deep percussion. In large tumors the compression of the lung may lead to shades of tympanitic notes.

Auscultation.—Over an aneurismal sac what one hears will depend very greatly upon the degree of lamination with fibrin and the state of the aortic valves. Usually the heart sounds are transmitted loudly into the sac, the first dull and thudding, the second clear, ringing, and accentuated, relatively louder, as a rule, than the first. This diastolic sound may be the only one audible, and when present is a very valuable diagnostic sign. Adventitious sounds are not always heard. It is surprising, indeed, in how many aneurisms a murmur is not heard. A systolic bruit is common, and it may be transmitted to the vessels of the neck. The diastolic murmur is less frequently heard, and is present when the aortic valves are insufficient or the ring dilated. Sometimes it is caused in the very large sac itself. A to-and-fro double murmur is not uncommon. A continuous humming-top murmur, with systolic intensification, is present when the sac has opened into one of the large vessels or communicates with one of the chambers of the heart.

A systolic murmur is not uncommon over the trachea, and David Drummund pointed out that it may sometimes be heard at the open mouth.

State of the Heart.—Large sacs of the arch displace the heart downward and to the left, and cause it to assume a more transverse position in the chest. This is usually very well seen in the *x*-ray pictures. A very large aneurism growing downward may gradually dislocate the heart and occupy its position, as in the remarkable case reported by Gee. Aneurism of the descending thoracic aorta growing forward may flatten the heart somewhat and give a widespread and very diffuse sort of pulsation in the cardiac area. With the coexistence of aortic insufficiency, dilatation and hypertrophy of the left ventricle are present, and associated conditions, such as arteriosclerosis of the small vessels and contracted kidneys, may cause hypertrophy. But, as a rule, the heart is not enlarged in aneurism of the aorta. Yet occasionally, without any obvious reason, the heart may be voluminous. The writer reported the case of a man aged forty years, with a large saccular aneurism of the descending aorta, in whom the signs of hypertrophy of the heart during life were very marked. At postmortem the organ was found to be greatly enlarged. There was no valvular disease. The left ventricle was much dilated and hypertrophied, the chamber measuring, from aortic ring to apex, 12 cm. and the walls from 15 to 20 mm. in thickness.

Symptoms.—*Of aneurism of the aorta in general:* In many cases the condition is *latent.* Those who have seen much medicolegal work appreciate the great frequency of sudden deaths from this cause in apparently healthy individuals. The latent aneurisms are the small, rapidly

growing sacs in or just above the sinuses of Valsalva. The small, dissecting aneurisms with rupture, more rarely the ordinary aneurism of the arch, reach a considerable size without symptoms or physical signs. It seems scarcely credible, and yet an aneurism of the arch may penetrate the chest wall and form a tumor the size of the top of a lemon without the patient suffering any serious inconvenience.

The symptoms and physical signs of thoracic aneurism are to a certain extent antagonistic. A patient with the most characteristic physical signs may have no symptoms; one with every symptom may have no physical signs. Hence, Broadbent's useful division into *Aneurism of Symptoms* and *Aneurism of Physical Signs*. As a rule, both features are combined. The symptoms may be considered under the three groups, functional, symptoms caused by compression, and certain special features.

(*a*) *Functional.*—A sac of moderate size interferes little, if at all, with the work of the heart, so that enlargement does not necessarily occur, and when present is usually the result of aortic insufficiency, relative or valvular. Palpitation of the heart, and irregular, unpleasant throbbing may be complained of. During a sudden exertion fainting may occur. Disturbances in the functions of the organs, due to lack of blood supply, are not very common. One carotid may be obliterated without any cerebral disturbances. Hemiplegia, however, may occur. The writer has never seen an instance in which imperfect blood supply to the upper extremities was associated with either paresis or intermittent claudication. But aneurism of the thoracic or abdominal aorta or its branches may be associated with intermittent claudication, and it was in a case of aneurism of the internal iliac that Charcot described first this condition in man.

The *pain* in aneurism is usually attributed to the stretching of the nerves about the aorta and on the sac, but it may be largely due to changes in the artery itself, which has a rich nerve supply. We know that local conditions in the intima may cause agonizing pain, particularly the plug of an embolus. The writer once went into a house for a consultation, a doubtful case, just as the young man had an embolism of the left femoral. He was howling in agony, and could not bear to have the spot touched. Thoma refers to the early pain in the chronic aortitis which leads to dilatation of the arch and attributes it to the involvement of the Pacinian bodies in the adventitia.

Alan Burns, too, called attention to the pain in arterial disease. Attacks of severe angina pectoris may occur in the early stages of aortic aneurism. The cases are met with in comparatively young men who have had syphilis, and the paroxysms may be of great severity and of frequent recurrence. The physical signs may be negative, and it may be a year or more before aneurism is suspected.[1] In other instances there are well-marked signs of aortic insufficiency. A feature of very great interest in certain of these cases is the complete disappearance of anginal attacks with the use of iodide of potassium.

[1] For a group of cases, see *Medical Chronicle*, 1905.

(*b*) *Symptoms of Compression.*—An aneurism may grow to a large size without causing inconvenience. Whether active symptoms of compression are caused depends on the situation of the tumor and on the direction of its growth. From the ascending and terminal portions of the arch tumors extending laterally are much less likely to interfere with neighboring structures, and the largest tumors arise from these portions. The space between the posterior wall of the sternum and the spine at the level of the aorta is only a few centimeters, so that aneurisms growing from the transverse portion of the arch cause early signs of compression.

The chief symptoms of aneurism are those of tumor, and arise from interference with neighboring parts by compression. The following are the more important structures involved: (1) *Nerve trunks and plexuses:* Pain due to stretching and pressure on the nerves is a common yet a very variable feature. A huge sac may erode the chest wall without causing any serious inconveniences. The pain presents very different characters. As already mentioned, there may be attacks of angina pectoris associated with an aortitis, and the beginning of the formation of the aneurism. More commonly, it is of a dull, heavy character, deep seated, and greatly aggravated in certain positions. It may present the features of a cervicobrachial neuralgia; in other cases, of an intercostal neuralgia of great severity and persistence. Sometimes the pain shoots down the arm, and there may be numbness and tingling as far as the finger tips. Erosion of bones is usually associated with pain of a very intense boring character, but the sternum and adjacent cartilages and ribs may be eroded and perforated without causing distress. On the other hand, the spinal column when compressed is a source of persistent and terrible pain. Sometimes it is of the well-marked character of nerve-root pains, such as we see in secondary carcinoma of the spine, but in other cases it is different—a deep-seated, boring intense agony only relieved by maximum doses of morphine. These terrible tragedies of pain are most common in aneurism of the lower thoracic and abdominal portion of the aorta. The corresponding skin areas of Head may be sensitive to touch, in the region of the nipple, along the left sternal border, and over the neck.

Compression or irritation of certain nerves may cause special symptoms. Irritation of the *phrenic* may be associated with hiccough. Symptoms arising from compression of the pneumogastric are not often met with. Some have attributed to this cause the attacks of nausea and vomiting which occasionally occur, and the recurrent dyspnœa, but this does not seem to be very likely.

Pressure on the *sympathetic* does sometimes occur with the characteristic features, namely, flushing of one side of the face with increased heat, sweating, dilatation of the pupil, and slight drooping of the eyelid. This is, however, a rare combination. It has already been mentioned that the difference in size of the pupils is most frequently a question of tension in the ophthalmic arteries. Unilateral sweating is probably the most characteristic sign of compression of the sympathetic. This interesting feature, first noted by Gairdner, is usually confined to the

sides of the face and neck, toward which the aneurism projects, and more frequently on the right side than on the left. The writer has seen it on the side opposite to that in which the aneurism is bulging, but it is not always possible to say how far the sac may extend on either side of the middle line, and it is a very short distance from the aorta to the cord of the sympathetic. The sweating may extend to the arm and side of the chest and the skin of the right hand may be like that of a washerwoman's. Instead of being flushed and of a higher temperature, the skin on the affected side may feel cold and be several degrees lower than the opposite side. The skin of the face may look pale, and sometimes the hand and arm of the affected side are quite pallid.

The Recurrent Laryngeal Nerve.—Pressure on this nerve is a common event in aneurism of the arch, around which the left nerve curves, and it may occur with very small tumors. The right nerve may be involved in a large sac springing from the ascending aorta and the transverse arch. The symptoms caused are very important: (*a*) Alteration in the voice, which has a cracked character; sometimes the change is very slight, but in others it is most striking. Actual aphonia is rare, although the voice may be reduced to a whisper. Most commonly the voice is that of a unilateral paralysis. (*b*) A peculiar quality of the cough, which becomes ringing, "brassy," or croupy. It differs from the cough of tracheal or bronchial compression, which is dry, harsh, and grating, and is usually accompanied with dyspnœa. (*c*) In rare instances there is painful spasm of the muscles of the larynx and pharynx, and even of the œsophagus. (*d*) Attacks of dyspnœa, which may occur with unilateral paralysis, are more common when both nerves are affected, as they may be by two aneurisms, or in rare instances by an ascending neuritis and extension to the nucleus of the other nerve.

Œsophagus.—Dysphagia is a very common and, with the small tumor from the posterior part of the arch, an early symptom. It is rarely extreme, but it may prevent the patient from taking solid food. Perforation of the œsophagus and fatal hemorrhage may occur without any previous difficulty in swallowing. The results of the compression may be necrosis of the wall without perforation. Ulceration may occur over the point of greatest compression. When the sac perforates directly into the gullet there is fatal hemorrhage; sometimes the orifice is temporarily blocked by a clot.

Trachea and Bronchi.—The most common and characteristic features of aneurism are associated with irritation and compression of the air passages. The condition may at first be mistaken for asthma. *Cough,* of the earliest symptoms, is due in a great many cases to tracheal irritation, more particularly when the sac is in the neighborhood of the bifurcation. When there is simple compression, anything that lowers the tension in the sac benefits the cough, and ten days in bed may cause its disappearance. On the other hand, the slightest exertion may bring it on. In other cases the cough is due to a tracheitis, and the mucous membrane is found swollen and reddened and there is a great increase in the secretion. There is a difference in the character of the cough in the two conditions. In one it is dry and wheezing, nothing is brought

up, but in the other there is a very large amount of expectoration. The peculiar, brazen quality of the cough in aneurism is laryngeal not tracheal.

Dyspnœa.—Aneurismal dyspnœa presents the following characteristics. In the first place there may be the ordinary shortness of breath associated with the growth of a large intrathoracic tumor, but without any signs of direct compression of the trachea. Aneurismal dyspnœa resulting from this cause is infralaryngeal and all grades are met with. In the aggravated cases there is an orthopnœa with prolonged inspiration, often noisy, sometimes with a marked stridor, or a fine sibilant sound. Expiration is shorter and not so noisy. While the difficulty of breathing is constant, there are paroxysms in which the intensity is greatly increased and the patient feels, as Morgagni expresses it, as though a cord was being tightened about the wind-pipe. Retraction of the tissues at the root of the neck, the epigastrium, and the costal borders is usually present. Gerhardt called attention to the limitation of vertical movement of the larynx in tracheal stenosis: "In spasmodic and stridulous breathing laryngeal movement of less than one centimeter is a certain sign of tracheal or tracheobronchial stenosis." Very often these patients are admitted to the hospital in terrible paroxysms, and it may not be easy to determine whether the narrowing is laryngeal or not. If a laryngeal examination can be made it is not difficult, but otherwise it is not at all easy. The cracked voice, the brazen character of the cough, the quality of the stridor, whether over the larynx or lower in the course of the trachea, the degree of movement of the larynx in inspiration, are important points.

Compression of Bronchus.—An aneurism may narrow one or other main bronchus without seriously compressing the bifurcation, or only the branch going to one or other lobe may be involved. This may produce a picture in which the true nature of the disease is obscured. In gradual compression the condition of atelectasis may follow with subsequent sclerosis. This does not often happen to an entire lung, but it may to a lobe or part of a lobe. The narrowing results in retention of secretion and intense bronchitis, sometimes with expectoration of large quantities of mucopus. Dilatation of the bronchi may supervene, but more common and deceptive is the gradual invasion of the lung tissue itself, so that the organ becomes consolidated, the bronchi filled with pus, sometimes quite inspissated, and the lung infiltrated, perhaps here and there a cavity formation. The whole process resembles tuberculosis, for which clinically the cases are mistaken. There may be areas of consolidation and bronchiectasis in both lungs as a result of tracheal compression. At the Montreal General Hospital the late George Ross used to speak of this condition as "aneurismal phthisis," and the writer has seen four or five cases in which the diagnosis of consumption had been made.

Lung.—The growing sac may push aside the lung and compress the upper lobe without causing anything more than slight atelectasis, expressed clinically by the very important physical sign of feebleness or absence of breath sounds. But the sac may grow directly into the

lung, the tissues of which form its actual wall. Under these circumstances, if the sac is small and grows from the terminal part of the arch into the left apex, and if hemoptysis is present, the case is of course mistaken for one of tuberculosis. The writer saw two such instances in 1907, one at the Royal Victoria Hospital, Montreal, with John McCrae, the other at the Radcliffe Infirmary, Oxford, with Dr. Mallam. In neither was there any suspicion of aneurism. In both there was fatal hemorrhage. In other instaces the aneurism grows into the lung, and in the formation of a large sac repeated small hemorrhages occur. Complete consolidation may follow. There is a specimen in the McGill Museum of an aneurism which occupies a large portion of the centre of the left lung, and which had become obliterated by thrombi.

Bloodvessels.—Considering how close in many cases the aneurism is to the great veins, it is surprising how rare are severe symptoms due to compression of the superior vena cava. The pressure may be exerted on the vena cava itself, on the innominate, or on one of the subclavian veins. It is not very uncommon to meet with congestion of the veins of the neck and head, and sometimes one or other arm is swollen. All this may disappear completely after a copious bleeding or after a week's rest in bed. The small aneurism of the ascending portion of the aorta growing to the right may compress the vena cava very early, even before physical signs are apparent. It is in this situation particularly that the most marked effects of compression from aneurism are seen. Narrowing of the lumen is the most common event, and throughout the course of the disease there is more or less fulness of the veins of the head and upper extremities. Rupture of the aneurism into the superior vena cava is followed by remarkable signs and symptoms, which will be discussed under the section of arteriovenous aneurism. The gradual compression may lead to thrombosis and complete obliteration of the superior cava. Of the 29 cases which the writer collected in a paper on obliteration of this vein, 4 were associated with aneurism. The picture is usually a very striking one, owing to the enormous development of the collateral circulation. This is carried on through a number of channels: (1) If the obliteration is above the point of entrance of the vena azygos, a large amount of blood from the arms and trunk finds its way into this vein through communications of the intercostals with the internal mammaries. (2) Over the surface of the chest the plexus of mammary veins enlarges and the subcutaneous tissues may be swollen, and the entire front of the chest is occupied by a system of greatly distended veins. These may be seen in and beneath the skin forming tortuous channels the size of the finger and converging to two or three large vessels which unite with the epigastrics. On the front of the abdomen are seen large convoluted vessels which empty below into the femoral veins. In some cases the venous plexuses are entirely subcutaneous. In others the veins of the skin itself are dilated and give the general surface a purplish red hue. So distended may the superficial mammary veins become that in the large sinuses thrombi form which may ultimately calcify, forming vein-stones. (3) Extensive communications exist between the deep cervical and the vertebral veins with the intercostals

and the whole network of veins along the front of the spine. These communicate freely with the branches of the azygos, or when the orifice of that is obliterated numerous channels are established between the lumbar vessels and the territories of the inferior vena cava.

The *inferior cava* is less often compressed. The *innominate vein* or *one subclavian* may be narrowed, rarely obliterated, causing great engorgement of the hand and arm. The *pulmonary artery* may be narrowed or perforated. Gangrene of the lung has been caused by compression of the vessels. *Compression of the vena azygos* may cause œdema of the chest wall or effusion into the right pleura. The *thoracic duct* may be involved in any part of its course, but symptoms due to this complication are rare. Morgagni noted the great dilatation of the abdominal lymph vessels with varices and lacunæ in a case of thoracic aneurism.

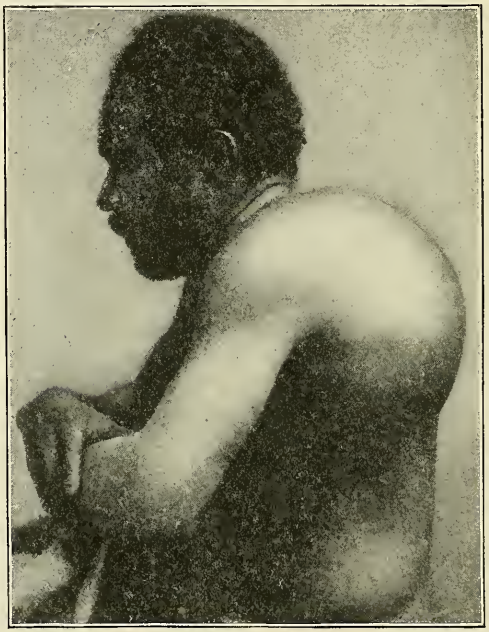
Spinal Cord.—In a few instances the bodies of the vertebræ have been destroyed and the spinal cord directly compressed by the sac, causing paraplegia. Rupture has occurred into the spinal canal. The paraplegia may be due to blocking of the aorta, which causes anemia of the cord such as follows ligation of the vessel experimentally.

Special Symptoms.—*Hemoptysis.*—Latent tumors growing backward from the transverse arch may rupture into a bronchus or the trachea, causing early and fatal hemorrhages. More frequently there are well-marked signs, and the bleeding may be of very different characters. With pressure and a granular tracheitis, bloody sputum may occur for weeks and gradually disappear. Brisk hemorrhage almost always comes from an open erosion, but it is not necessarily directly fatal. The laminæ may be within the lumen of the trachea, and through small chinks and crevices the sac may "weep" at intervals, or continuously for weeks and months. There are remarkable cases in which in the course of a few weeks numerous hemorrhages occur. Death may not follow for months or even years. A patient of Dr. Fussell, with aneurism, upon whom the writer lectured in Philadelphia, lived for four years after a severe hemoptysis. The famous surgeon, Liston, had, in July, 1847, a feeling of constriction at the top of the windpipe and slight difficulty in swallowing. A profuse hemoptysis, 30 to 40 ounces, nearly killed him. Liston himself suspected aneurism, but neither Watson nor Forbes could discover anything in his chest. He was greatly relieved by the hemorrhage. In October the symptoms returned, but it was not until December 6 that he died in a paroxysm of dyspnœa. The trachea was perforated, but the orifice was blocked by firm laminæ of fibrin. The small tumors growing upward into the apex of the lung on either side may be associated with repeated hemorrhages, and the diagnosis of tuberculosis is usually made.

Modes of Perforation.—1. *External.*—As the sac enlarges, the wall of the thorax is perforated, the tumor appears beneath the skin, and may reach an enormous size. Finally the skin becomes reddened, a spot of necrosis forms, slowly increases, the aneurism at first "weeps," and finally bursts with fatal hemorrhage. Considering the large number of cases in which the chest wall is perforated and the skin eroded, fatal hemorrhage from this cause is comparatively rare. The sac may be very

voluminous, as represented in Fig. 49, which shows a negro with an aneurism of the descending thoracic aorta. Lined as it is with firm thrombi, the sac may perforate the skin without any hemorrhage, and the patient may live for months and die of internal rupture. William Hunter reports the case of a man with an aneurism perforating to the right of the sternum, in whom the sac bled for weeks at intervals from an orifice plugged by a coagulum which protruded and retracted with the systole and diastole of the heart. A sudden cough burst out the plug, and "the blood gushed out with such violence as to dash against the curtain and wall, and he died not only without speaking but without a sigh or groan." The writer has seen a sac "weep" for months; in one patient it became

Fig. 49



Aneurism of the descending thoracic aorta. (Photograph taken by I. C. Skinner, M.D., of Selma, Alabama.)

infected with the *Bacillus capsulatus aërogenes*, and the patient died of a general infection. It is remarkable how much a sac presenting externally may vary with the condition of the patient. Prolonged rest in bed, bleeding, wiring, may reduce the size, and we have had instances in which the external tumor has completely disappeared. Great relief may be obtained by a carefully adapted bandage, but it must not be too tightly applied. Some years ago the writer saw a physician with a very large sac projecting beneath the right clavicle, for the support of which he wore a very ingeniously devised pad. By far the most common site of external perforation is to the right of the sternum. A prominent sac may disappear completely after external rupture (Morgagni).

2. *Perforation into the Trachea or Bronchi.*—Already under the section on hemoptysis this has been referred to, and it is perhaps the most common of all localities. It usually takes place in the lower third of the tube, and the orifice may be single or double. By pressure the wall is gradually eroded; a small, rapidly growing sac may perforate before there have been any special symptoms; more commonly there is an irritative cough and the characteristic dyspnœa. As already mentioned, the perforation is not necessarily fatal, and the symptoms may be, as in Liston's case, greatly relieved by the hemoptysis. The orifice may be closed by firm thrombi, and months or even years may elapse before final perforation takes place. In one case under the care of the writer there were two perforations, and the patient died of a third one into the œsophagus. The left bronchus is more frequently involved than the right, more frequently, indeed, than the trachea itself.

3. *Rupture into the Lung.*—The lung tissue itself may form a large part of the wall of the sac, and it is particularly aneurisms of the terminal portion of the arch and the first part of the thoracic arch that tend to grow into the upper lobe or invade the central portion of the lung. Slight and recurring hemoptysis may occur, and the diagnosis of tuberculosis is sometimes made. The writer has not met with an instance of fatal hemorrhage unless the sac opened into a bronchus. There may be a very large sac almost completely consolidated within the lung substance itself. A brief reference to the Index Catalogue (both series) under Aneurism gives a good idea of the great frequency of rupture into the trachea, bronchi, and lungs.

4. *Œsophagus.*—This is not so common, and there were only 9 cases among 226 of Crisp's series. The rupture takes place usually by gradual erosion, which has sometimes been preceded by local necrosis and gangrene. Dysphagia usually precedes the perforation, but in small sacs the rupture may take place suddenly in individuals in excellent health. The writer has reported such an instance in a woman, aged thirty-five years who died in syncope. The aneurism was only 5 by 5 cm. in extent, and communicated by a linear slit 1.5 cm. in length with the lumen of the aorta. It is not uncommon to find the œsophagus stretched over the wall of the sac, closely adherent, and the muscular layers much wasted. The cases in which ulceration and gangrene precede the rupture are of special interest, since cancer of the œsophagus may be suspected. In the Index Catalogue, second series, there are 17 cases of perforation of the œsophagus noted. It may take place simultaneously into the bronchus or trachea and the œsophagus. The coats of the œsophagus may be split and the blood pass between them and burst into the stomach, as in a case reported by Frederick Taylor.

5. *Rupture into the Pericardium.*—This is one of the common causes of sudden death in robust, apparently healthy men. Medicolegal records of large cities show the very great frequency of this accident. The perforation may be of a small sac of one of the sinuses of Valsalva, or there is a tear of the intima with a small dissecting aneurism and rupture of the external coat, or the intrapericardial portion of an aneurism of the ascending portion of the arch gives way. The rupture may be

pinpoint in size or a large transverse tear. In a few cases a small mycotic aneurism bursts. Death takes place with suddenness. There are instances on record in which the patient has lived for some hours.

6. *Other modes of rupture* are on record—into the anterior or posterior mediastinum, the muscles of the neck, and into the vessels and heart.

The conditions under which rupture may occur are important. When the individual is at rest or sleeping the fatal event may happen. More often the rupture is during some exertion, while straining at stool, or in a scuffle, or while under an anesthetic. The dangers of coitus were referred to by Morgagni, who says that many patients die in this way.

Pleura.—Hydrothorax is not very uncommon, and may be a pressure effect on the azygos veins, and it is more frequent on the right side than on the left. It may complicate the diagnosis, and sometimes recurs repeatedly. The bloody serum may be present as an effect of pressure on the veins. Acute pleurisy, usually tuberculous, may be a terminal event. In a few cases aneurism has been complicated by empyema.

Descending Thoracic Aneurism.—Aneurism of this portion presents a few special features. It is rarer than in the abdominal aorta. If we add the statistics of Crisp, Lebert, and Myers, this portion was involved in 49 against 159 of the ascending, 113 of the arch, and 83 of the abdominal aorta. It was involved in only 3 out of 64 cases of aneurism of the aorta among 2200 autopsies at the Johns Hopkins Hospital.

Symptoms.—There may be no symptoms whatever; the first indication may be a sudden syncope from internal hemorrhage, vomiting of blood or hemoptysis. Three out of the 14 cases described by the writer were latent. A second feature is the intensity and the peculiar character of the pain. Owing to the close relation of the aorta to the spine and the frequency with which the tumor grows backward, pain in the back and along the sides from pressure on the nerves is usually *the symptom* of the case. Erosion of the spine to an extensive degree may occur without pain, but this is rare. Some of the patients are never without it for a moment, except when under the influence of morphine, of which one patient took for a long period as much as between 30 and 40 grains a day. There may be nothing in the case but the *pain*. Perhaps to the left of the spine there is heard a soft systolic murmur, or there are feeble breath sounds in the left lung, but it may be months before there are any physical signs. The third special feature is the prominence of the pulmonary symptoms due to pressure either on the lung itself or on the main bronchus. Hemorrhage occurred in only 3 of 14 of the writer's cases; it may be due to a direct weeping through the lung tissue, or it is a terminal hemoptysis due to perforation of a bronchus. The whole lung may be compressed by an enormous aneurism, or the bronchus may be blocked with the production of purulent bronchiectasis, and the patient may present the symptoms of extensive destruction of the lung or in slight compression, the inspiratory murmur may be normal the expiratory interrupted. Some writers have referred to pressure on the gullet as a special feature of aneurism of this part. It was present in only two of the writer's cases and in only one did rupture take place into the œsophagus. The tumor may grow to an enormous size, as in

the famous case[1] in which the patient lived for twelve years and the greater part of the left chest was occupied by a non-pulsating tumor.

Abdominal Aorta.—The *incidence* varies in different localities. Sixteen cases occurred among about 18,000 admissions to my wards. The ratio of abdominal to thoracic aneurism was 1 to 10. Among 2200 autopsies at the Johns Hopkins Hospital there were 11 instances of aneurism of the abdominal aorta. The Guy's Hospital figures were collected by the late J. H. Bryant for the years 1854–1900; among 18,678 necropsies, there were 325 cases of aneurism of the aorta, of which 54 (or 16 per cent.) were of the abdominal portion. Males are much more frequently attacked than females. Only 2 of the writer's 16 cases were females, and all statistics indicate this infrequency in women, a point to be borne in mind as the throbbing aorta is so much more common in them. A majority of the patients are young men. In 63 per cent. of Bryant's series they were under forty years of age, and in 2 the disease began before the twentieth year.

It is most frequent in the upper portion of the abdominal aorta, and it is usually of the saccular form. Rupture into the retroperitoneum is common, forming the diffuse or false aneurism, which may reach a colossal size. A huge sac may occupy one-half of the abdomen and project in the back, forming a tumor the size of the head.

Symptoms.—In no situation are the symptoms of aneurism so obscure, and even when pulsation is present the diagnosis is not easily reached. This is well brought out by Bryant in the analysis of the Guy's Hospital statistics: "A correct conclusion during life as to the nature of the disease was arrived at in 18 only out of the 54 cases on which this lecture is based, an analysis showing that an abdominal tumor was detected in 31, pulsation in 35, expansile pulsation in 8 only, and in 26 a systolic murmur. Incorrect diagnoses of a variety of diseases were made, including malignant tumors lying in front of the aorta, renal calculus, lead colic, spinal caries, sarcoma of the kidney, nephritis, perinephritis, pneumothorax, pleuritic effusion, epithelioma of the œsophagus, malingering, chronic intestinal obstruction, etc."

Pain, usually the first indication, remaining throughout the special feature and reaching an intensity not met with in any other disease, presents three features of importance. It is usually of a constant, dull, boring character, particularly when the aneurism has eroded the spine. There may be paroxysms of the greatest intensity for months before a diagnosis is made. The pain may be segmental with hyperesthesia of the skin fields; there may also be transitory paresthesia in the lower limbs. And lastly, when the aneurism ruptures into the retroperitoneal tissues, the pain with other features may give to the case the characters of the acute abdomen. The writer knows of at least four cases in which the operation for appendicitis was undertaken. Nausea and vomiting may be early and severe symptoms. In one of the cases there was great dilatation of the stomach due to pressure upon the duodenum. In another there was great dilatation of the œsophagus owing to pressure

[1] *Deutsch. Arch. f. klin. Med.*, Band xix.

at the cardiac end of the stomach; an aneurism of the hepatic artery recently recorded gave rise to chronic jaundice and intestinal hemorrhage. Compression of the splenic vein may cause enlargement of this organ. The aneurism may rupture into the stomach, duodenum, or colon, into the retroperitoneal tissues, which is the most common mode, or pass upward and rupture into the pleura. The peritoneum, the bladder, or the inferior vena cava may be perforated. Embolism of the aorta below the sac may occur, or one femoral may be blocked with the result of gangrene of the leg. The writer has not found a case of external rupture. Embolism of the superior mesenteric artery may occur with infarction of the bowel.

ARTERIOVENOUS ANEURISM

A communication between artery and vein with or without an intervening sac. In the one case the term *aneurismal varix* is applied, and in the other, when a sac is formed between the two vessels, *varicose aneurism*. Although chiefly a surgical affection, met with in the peripheral arteries, it occurs in the internal vessels and has important medical bearings.

William Hunter, in 1757, described a particular species of aneurism following the simultaneous opening of an artery and a vein, in consequence of which the latter became dilated and varicosed, and had a pulsatile, jarring motion with a hissing noise. He described several cases which occurred from unskilful venesection at the bend of the elbow. The observation was not new; from the time of Galen it has been known the aneurism might follow unskilful venesection at the bend of the elbow, but Hunter recognized it as a special form. The monograph of Breschet[1] and the work of Broca[2] are of great value; indeed, there is not a better description in literature than that given in the latter.

Traumatic.—These cases have a surgical rather than a medical interest. While in the internal vessels the communication is usually direct, in the larger external trunks there is more often the intervention of a sac. Formerly, venesection at the bend of the elbow was the common cause, and the communication existed between the brachial artery and the vein. Now the cases are chiefly the result of stab wounds and of bullet wounds. Military surgeons state that with modern bullets the lesion has become more common. The experience of the South African War is given by W. F. Stephenson[3] in a Government Report, and of the Russo-Japanese War by Siago.[4] The work of Matas and the technique in arterial surgery developed by Carrel (Rockefeller Institute Publications, New York) should lead to greatly improved results.

The vessels most commonly involved are the femorals, subclavians, axillaries, brachials, and popliteals. So much higher is the arterial than the venous blood pressure, that when an artificial communication exists between vein and artery, the former with its branches becomes permanently distended. The obstruction offered to the free return of blood makes

[1] *Memories de l'Academie de Medecine*, 1833.
[2] *Des Aneurismes*, 1856.
[3] *On the Surgical Cases, etc.*, 1905.
[4] *Deutsch. Zeit. f. Chir.*, Band lxxxv.

the distension of the collateral veins still more marked. The orifice of communication may be small and slit-like or oval, and, as already stated, a sac may exist between the two vessels. In many cases the communication is direct. The anatomical changes are chiefly in the veins, which become greatly enlarged, varicosed, with thickened walls, and frequently present flakes of atheroma in the intima.

The three distinguishing features of this aneurism are: (1) The swelling of the part caused by the distension of the veins. When only the deeper vessels are involved, they may not be visible externally, but, as a rule, large varicose vessels are to be seen. In the case of arteriovenous aneurism of the femorals or iliacs the engorgement of the veins may be enormous. In no condition do we see such huge saccular dilatations. In the annexed figure one of these is shown forming a large tumor just above Poupart's ligament. In the veins and in the large venous sinuses pulsation may be visible, but, except close to the arteries,

FIG. 50

Arteriovenous aneurism of the iliac vessels.

it is not forcible. (2) On palpation a vibratory thrill is felt, of maximum intensity over the position of the orifice, but widely diffused, and in the case of an aneurism of the axillary vessels, to be felt as low as the palm of the hand, and in the case of an aneurism of the femoral vessels, to be felt as low as the foot, and even to the crown of the head. In the large bunches of subcutaneous veins, the calcified walls and occasionally phleboliths may sometimes be felt. When a sac intervenes between the artery and the vein, it may be felt, and presents aneurismal pulsation, forcible and expansile. (3) On auscultation there is heard everywhere over the aneurism and up and down the limb a "bruit de diable" of great intensity. An interesting point is the fact that one of the earliest instances recorded of auscultation was in a case of varicose aneurism reported by Mr. White, a surgeon at York, in a letter to William Hunter. He states, "On applying my ear to the tumefied basilic vein, the pulsation, tremulous motion, and noise are distinctly perceived." The murmur is continuous, with systolic intensification.

The condition may remain stationary for years. Spontaneous healing does not occur. There may be progressive increase in the veins, leading to enormous varicosity and to great disability, and it is for this that relief is sought. This progressive enlargement of the veins is really the chief danger. At the age of fifteen years a young man fell and forced a lead-pencil into his axilla. This was followed by a gush of blood, and in a few moments the arm began to swell and became black and blue to the wrist. He gradually got better, but there was always a swelling in the armpit and infraclavicular region. It did not, however, interfere with his work or exercise. Ten years after, when the writer saw him, he had well-marked signs of arteriovenous aneurism of the axillary vessels. He was athletic and had rowed in races. He has been seen at intervals since, and there is practically no change in the arteriovenous aneurism. He subsequently served in the South African War, and was invalided for aneurism. The writer heard of him last twenty-three years after the accident. Broca mentions two interesting circumstances: the greater growth of the limb below a femoral aneurism of this kind, and the increased growth of hair on the skin, both the result of the venous engorgement.

Internal Arteriovenous Aneurism.—While rare, this form is of great interest.

1. **The Aorta and Superior Vena Cava.**—This gives a very remarkable picture. One morning, at the hospital of the University of Pennsylvania, a Chinaman, aged forty-eight years, was admitted in a condition of extreme dyspnœa, with the skin of the face and arms cyanosed, the eyes suffused, and the whole upper part of the body engorged and œdematous. He presented an extraordinary appearance on account of the contrast between the upper and lower part of the body. The writer had never seen a similar picture. The case, which was under the care of his colleague, Pepper, excited a great deal of interest. The most striking physical signs were: a loud thrill over the precordia, a continuous "humming-top" murmur, with marked systolic intensification, which was heard best over the base, and was transmitted into the vessels of the neck and down the arm as far as the elbow. The patient lived for two weeks, with extreme orthopnœa and an increase of the œdema of the upper part of the body; so intense was the infiltration of the blood-vessels of the conjunctiva that blood oozed. The writer made the autopsy with Crozer Griffith, who, in conjunction with Dr. Pepper, has reported the case very fully.[1] A small aneurismal sac of the ascending aorta had perforated the superior vena cava. A second case at the Johns Hopkins Hospital, in 1899, presented an almost identical appearance.[2] The patient's face was enormously swollen and blue looking, like a man who had been strangled. There was the same extraordinary contrast between the upper and the lower part of the body. In the second right interspace was heard a loud, continuous murmur, with marked systolic intensification. The patient had had syphilis two years

[1] *Transactions of the Association of American Physicians*, 1890, vol. v.
[2] Notes on Aneurism, *Journal of the American Medical Association*, June 7, 1902.

before, and although there were no signs of aneurism, there could be very little question as to the nature of the trouble.

The first report of a case of this kind was by John Thurnam,[1] whose paper on these internal arteriovenous aneurisms was the first and is one of the best in literature. Pepper and Griffith collected 28 cases of this lesion, and there have been a good many reported since the appearance of their paper. The symptoms are quite distinctive: (1) cyanosis, œdema, and distension of the veins of the upper part of the body, with signs of obstruction in the tributaries of the superior vena cava; (2 suddenness of the onset of the symptoms; (3) evidence of the presence of a tumor in the thorax; (4) the existence of a murmur characteristic of a communication between an artery and a vein.

2. **Aorta and Pulmonary Artery.**—This is rather more frequent, and the condition has been carefully studied by Frederick Taylor and Gairdner; Kappis,[2] from Baümler's clinic, has collected 30 cases. The symptoms are not unlike those of perforation into the superior vena cava and are characterized by a sudden onset with cyanosis and œdema, which, however, are not so accurately limited to the upper half of the body, as in the cases of perforation into the superior vena cava. Signs are usually present of aortic aneurism. A thrill is felt over the base of the heart, and there is a loud humming-top murmur, with maximum intensity to the left of the upper part of the sternum. Thurnam has reported a case of perforation of an aneurism into the right ventricle, which had a murmur of the same character in the second left intercostal space.

Perforation of an aneurism into one of the branches of the pulmonary artery gives rise to a similar murmur. In a case admitted to the wards in 1901, with aneurism of the thoracic aorta, there was a feeble thrill and very loud continuous murmur occupying the entire cardiac cycle, with marked systolic intensification. This was heard best to the right of the sternum. The aneurism was found to have compressed the right lung, which formed the posterior wall of the sac into which one of the main branches of the pulmonary arteries had opened.

3. **Abdominal Aorta and Inferior Vena Cava.**—This is not so common. Thurnam reports 3 cases in his paper, in all of which the perforation had taken place from an aneurism. In 1 case in J. H. Bryant's series at Guy's Hospital the vena cava was perforated. As a rule, the symptoms are well defined, namely, those of aneurism of the abdominal aorta with sudden onset of swelling and cyanosis of the lower extremities, and œdema of the lower half of the body. The characteristic humming-top murmur is heard over the tumor.

Diagnosis.—From Dynamic Dilatation of the Aorta.—That the throbbing, distended aorta, the condition of preternatural pulsation, as Allan Burns calls it, may lead to diagnosis of aneurism is an observation that dates from the time of Morgagni. It is met under the following conditions:

1. *Aortic Insufficiency.*—In young persons the degree of dilatation caused by the propulsion of a large volume of blood from a powerfully acting heart may be extraordinary. It is not very uncommon to see a

[1] *Medico-Chirurgical Society's Transactions*, 1840, vol. xxiii, p. 323.
[2] *Deutsch. Arch. f. klin. Med.*, Band xc, 1907.

slight throbbing of the aorta to the right of the sternum in these cases. Occasionally in a young man, when the insufficiency is extreme, and if anemia is present, the degree of throbbing and the extent of visible impulse in the second and third, or in the first and second right interspaces almost compels the diagnosis of aneurism; and yet postmortem the aorta may not be beyond the ordinary size. Much more commonly the mistake arises from the throbbing and dilatation of the innominate and the right carotid. Corrigan calls attention to this in his original paper: "So strong were the pulsations for years in the region of the arterio-innominate that until the examination after death there was never even a doubt expressed that the case was not aneurism." Many cases of this sort have gone into literature as aneurism. In 1886, Hare[1] reported an interesting case of this kind. A girl of seventeen had had repeated attacks of rheumatic fever, and she had been made the subject at several clinics, at which no doubt had been expressed as to the existence of aneurism. Nor is this to be wondered at when one reads Hare's statement: "There was an egg-shaped protrusion in the supra-sternal notch, very expansile and bulging with each systole of the heart, and the dilatation extended well up into the vessels." There was great hypertrophy of the heart, a double aortic bruit, and a Corrigan pulse. I had repeated opportunities to examine the patient; it was not a case of throbbing of the innominate and the right carotid during ventricular systole, but there was a prominent, dilated tumor to be grasped between the fingers just above the sternal notch. Having had a lesson in a somewhat similar though not so exaggerated a case, I had learned to be very chary in making the diagnosis of aneurism in young persons with aortic insufficiency. At the postmortem it was not a surprise to find the condition had been one of simple dynamic dilatation. The heart was enormously enlarged, there was an extreme degree of insufficiency of the aortic valves, the arch of the *aorta did not admit the index finger, nor the innominate the little finger.* It is important to bear in mind that there may be permanent fulness of the vessel, so that there is a tumor-like dilatation left above the sternal notch or the right sternoclavicular articulation. Many of the cases of so-called aortitis and aneurism in young persons following rheumatic fever are of this nature.

2. *Dynamic Dilatation in Neurotic Conditions.*—In hysteria, in neurasthenia, and in Graves' disease the throbbing vessels may lead to diagnosis of aneurism. It is not often that the dilatation and pulsation is of the arch. Bramwell, in his work on *Diseases of the Heart*, p. 723 has reported a remarkable instance in which "pulsation and dulness in the region of the heart were so distinct as to lead Dr. Murray, of Newcastle-on-Tyne, whose diagnostic ability generally, and in aneurism in particular, is well known, to believe that an aneurism of the ascending portion of the arch of the aorta was probably present." Within a few months these physical signs "completely disappeared."

Some years ago the writer was consulted by a clergyman for aneurism of the aorta which had been confirmed by one or two physicians, and

[1] *New York Medical Record*, 1886, vol. xxix, p. 558.

he brought an *x*-ray photograph. He was extremely neurotic, had an unusual degree of vascular excitement, throbbing of the subclavians and carotids, and a general jarring of the front of his chest. The *x*-ray photograph suggested a moderate dilatation of the arch. The condition had lasted for a couple of years, and he had become almost incapacitated. A positive assurance that he had not aneurism was followed by an extraordinary lessening of the abnormal pulsation. It is more particularly in the abdominal aorta that the abnormal aortic pulsation leads to error in diagnosis. The subjects of this remarkable pulsation are usually neurotic, sometimes definitely hysterical. They complain of pain in the back and at the occiput, and have the usual symptoms of nervous exhaustion and debility, but the special feature upon which all their feelings centre is the throbbing in the abdomen, which may be so severe as to interfere with their sleeping or even with the taking of food. In extreme cases there are pain, shortness of breath, and even remarkable attacks of hematemesis. It is stated that Hippocrates had noticed this pulsation, but to Morgagni we owe the first accurate description. Allan Burns[1] gives a very careful account of the condition, and quotes from Albers, of Bremen, a remarkable instance in which, associated with the throbbing, there was passage of dark blood in the stools. The association of small hemorrhage from the stomach and intestines has been described by Sidney Phillips,[2] but the writer has seen no reported case more remarkable than that of Albers. The girl was excessively neurotic, had fainting fits, great palpitation in the abdomen, and an astonishing degree of violent pulsation. She had passage of blood from the bowels, and the diagnosis of aneurism was made, but a Dr. Weinhalt, who was called in, said he doubted if the pulsations proceeded from aneurism, as he had read of similar cases in Morgagni.

The points to be borne in mind in these cases are: (1) That the pulsation occurs in nervous or hysterical women, or in neurotic or hypochondriacal males. In mild forms it is common. (2) The subjective sensations may be pronounced: pain, abdominal distress, nausea, sickness, constipation, and, in some instances, the vomiting of small quantities of blood and the passage of blood in the stools. (3) The degree of visible and palpable pulsation may be extreme. The abdominal aorta is easily palpable and may be grasped in the fingers. It is sometimes tender. No definite tumor is felt. With much anemia a thrill may be present. A soft systolic bruit may be heard, even without any pressure of the stethoscope. A mistake is not likely to occur if it is remembered that no pulsation, however forcible, no thrill, however intense, no bruit, however loud, singly or together, justify the diagnosis of an aneurism of the abdominal aorta, but *only the presence of a palpable, expansile tumor.*

3. *In Anemia.*—In extreme anemia from any cause the bloodvessels throb in a remarkable manner, and may suggest aneurism. This is not often the cases in the thoracic aorta and its branches, but in the abdominal aorta it may be extreme. There are conditions, indeed, under which the diagnosis of aneurism seems forced upon us. The writer has often

[1] *Observations on Diseases of the Heart, etc.*, 1809.
[2] *British Medical Journal*, 1887, vol. ii.

referred to an interesting experience of this kind in a case seen in 1885 with Dr. Whiteside. A large, stout man, aged forty-five years, had had for some months dyspepsia and pain in the abdomen. He had become very anemic, and the day before he was seen he had an increase of the pain. When examined he was sweating, pale, and the large, fat abdomen throbbed in a most extraordinary manner. The shock of the impulse was communicated to the patient's body, was visible everywhere from head to foot, and standing against the foot of the bed one could feel distinctly the jarring impulse communicated to it. On palpation the throbbing was violent with each systole, but it was trifling in comparison with the extent of visible pulsation. There was a loud systolic murmur, but no thrill. That evening he passed a large quantity of blood from the bowels, and though a definite tumor could not be felt, it was thought that the diagnosis of aneurism was certain. The postmortem showed a duodenal ulcer placed directly upon the pancreas. The aorta was normal. In pernicious anemia in the vessels of the neck and in the subclavians the throbbing may be so violent as to suggest aneurism.

From Other Tumors. — These may be subcutaneous, of the chest wall, or internal. (*a*) *Subcutaneous:* It does not often happen that a tumor beneath the skin on the chest wall is mistaken for aneurism. The suspicious ones which have come under my notice have been associated with necrosis of the sternum and the formation of the cold tuberculous abscess just to the right of it. There may be communicated throbbing, more particularly if the abscess has lasted long and there is periostitis of the posterior part of the sternum directly over the aorta. There may then be a definite jarring which is visible in the tumor. The points of difference are, however, very clear. The abscess tumor is softer and there is not an expansile, forcible impulse. The shock of the heart sounds is not felt, and there is no murmur. More confusing are the rare instances in which the *empyema necessitatis* pulsates. Here, too, the projecting tumor between the ribs has not a strong, heaving, expansile pulsation, but it is a diffuse throb. Then the signs of empyema are usually very clear, and, if in doubt, the needle may be inserted.

The ruptured aneurism of the abdominal aorta may form a very large tumor in the back, or the blood may pass down and form a mass in either iliac fossa, which may be mistaken for abscess or for appendicitis. Nowadays, with the frequency of abdominal operations, the mistake is not uncommonly made. The writer knows of four instances in which under these circumstances operation was performed, thrice for appendicitis, once for supposed abscess. As already mentioned, in some of the very large diffuse aneurisms of the abdominal aorta there may be little or no pulsation. The older authors mention many instances in which aneurism was opened in mistake for abscess. Ambroise Paré mentions a case of a priest in whom a barber surgeon had opened an aneurismal sac, and the patient bled to death. Morgagni also gives a case.

(*b*) *Of the Chest Wall.*—It does not often happen that a tumor of the chest wall is mistaken for aneurism. Osteosarcoma of the sternum or myeloma of this bone or of the rib may form a tumor to which a jarring

impulse is communicated. A vascular osteosarcoma of the sternum may have a very deceptive pulsation of its own, but the writer has not met with any such case and in pulsation of a rapidly growing tumor of the rib, the other circumstances left no doubt as to its nature.

(*c*) *Internal.*—Since the symptoms caused by an aneurism are those of tumor, it is not surprising that difficulties arise in mediastinal and other growths, but these difficulties have been greatly diminished with the aid of the *x*-rays. In two groups of cases error is possible. (1) The *small, solid growth* in the posterior mediastinum connected with the glands or with the œsophagus, which presses upon the windpipe, causing cough and orthopnœa and perhaps paralysis of the left recurrent nerve, gives a clinical picture identical with that of deep-seated aneurism. Nowadays even a very small aneurismal sac may be recognized with the *x*-rays. In a case of mediastinal tumor which gives only symptoms, that is to say, when there is orthopnœa and urgent distress, but nothing to be made out on examination by ordinary means, aneurism is much more likely than new growth. Occasionally the small tumor of the œsophagus is mistaken for aneurism. The statement is made that an œsophageal bougie, used for purposes of diagnosis, has been thrust into an aneurismal sac, but the writer has not found the record of such a case. The confusing circumstances are those in which there is difficulty in swallowing, attacks of dyspnœa, stridulous cough, and paralysis of the left vocal cord. When the œsophageal tumor is just at the bifurcation of the trachea it may form a small, hard mass involving the recurrent laryngeal and causing great difficulty in diagnosis. In a case of A. L. Scott's at the Pennsylvania Hospital, Philadelphia, in which the tumor occupied this situation, even with the *x*-rays it was not easy to determine the nature of the shadow just to the left of the vertebral column. An important point in the diagnosis of new growth is the age of the patient, which is more likely to be advanced. In the small tumor, whether of glands or gullet, the cervical lymph glands may not be involved.

The voluminous *intrathoracic tumor* growing from mediastinum, lung, or pleura may offer great difficulty. When situated over the aorta or over the heart, particularly to the left of the sternum, the communicated pulsation may be most deceptive, the heaving quite localized, and there is usually a bruit. There is never the strong expansile impulse, felt directly beneath the fingers, and upon this, not upon the extent of visible or palpable impulse, stress should be laid. With venous obstruction and the anterior wall of the chest œdematous and congested, the difficulty may be very great indeed, and the associated features of the case may be more helpful than any other. An enlarged gland above one clavicle or in the axilla, the mode of onset, the age, sex, the history of syphilis, are all important elements. The *x*-ray examination is most helpful in this group, as the outline of the pulsating aorta and heart may be differentiated from the lighter shadow cast by the tumor. Not all patients with aneurism, even due to syphilis, give a positive Wassermann reaction.

On the other hand, the huge chronic thoracic aneurism may simulate tumor, as the lamination may be so dense that pulsation is absent. In

a famous case,[1] Oppolzer diagnosed aneurism and Skoda tumor. The left half of the thorax was flat and there was no pulsation. The patient lived twelve years. The sac filled the greater part of the left chest. Aneurism and sarcoma may occur together, as in a case reported by Virchow in which the two were in direct connection.

From Other Forms of Pulsatile Tumors.—Not every abnormal pulsation indicates an aneurism. It may be well to mention the various forms of pulsatile tumors: (*a*) *Erectile tumors:* The diffuse angioma, in which all the vessels, arteries, capillaries, and veins are involved, forms a red- or violet-looking tumor when the skin itself is involved (which is usually the case), but sometimes it is entirely subcutaneous. The pulsation is diffuse, and a bruit is heard over the tumor. (*b*) Cirsoid aneurism, in which the arteries are chiefly involved; and in the recognition of this form there is rarely any difficulty. (*c*) Ordinary aneurism, true or false. (*d*) The arteriovenous aneurism. (*e*) The very vascular malignant tumors.

The last is the form of pulsating tumor which may be confused with aneurism. Rapidly growing tumors of bone and vascular sarcomata of the abdomen may present an expansile impulse, usually better felt than seen, but occasionally very marked on inspection. The writer remembers only two instances in which the extent and force of the pulsation led to error in diagnosis. One was a man with a large, rapidly growing sarcoma of the upper part of the thigh bone, in which the pulsation was so pronounced that the femoral artery was believed to be involved. The other was an instance of a large sarcoma, probably growing from the retroperitoneal glands, which had a forcible expansile pulsation, and a loud bruit could be heard. In the case of tumors of bone, either in the extremities or in the head, there should rarely be any difficulty; but the pulsating sarcoma in the abdomen is not so easy, particularly when one bears in mind the frequency with which diffuse aneurism of the abdominal aorta has been mistaken for tumor. The important point is the character of the pulsation, which may be diffuse, even expansile, but rarely conveys to the hand that sense of force and strength communicated directly from an aneurism of the aorta or of one of the larger vessels. The bruit over the aneurism is usually louder, but it must be borne in mind that when the sac is very large and filled with masses of coagulum there may be no bruit.

Aneurisms Which do Not Pulsate.—There are two conditions in which an aneurism does not pulsate: (1) When a sac is obliterated with laminated fibrin. Sometimes met with in aneurism of the aorta, this is much more frequent in the popliteal and femoral vessels. In the latter regions it is a serious matter, as the leg may be amputated under the belief that the tumor is a sarcoma. Such an instance was seen in Montreal, in which there was a very large mass in the popliteal space which had neither pulsation nor bruit, but proved on dissection after amputation of the leg to be a completely obliterated aneurismal sac.

[1] *Deutsch. Arch. f. klin. Med.*, Band xix, p. 623.

A remarkable case is reported by Hulke[1] and a sequel is given by Baker[2] in his paper "On Aneurisms Which do Not Pulsate." A huge tumor, which proved at postmortem to be an aneurism, occupied the left side of the neck from the trachea to the vertebræ, passed behind the clavicle, filling the axilla, and passed through the superior aperture of the thorax into the left pleural cavity, occupying its upper third and compressing the lung. It sprang from the left subclavian artery. The large aneurism referred to in the previous section did not pulsate. (2) The second condition in which an aneurism may not pulsate is when it ruptures into the neighboring tissues, forming a diffuse tumor. This may occur in the neck, as in the case reported by Hulke and Baker, but it is much more common in the abdomen. As in two cases which the writer has reported, the tumor may be of enormous size and present slight, almost imperceptible pulsation. Sometimes no impulse whatever is to be felt. More particularly is this the case when the tumor extends rapidly in the flanks, forming a large solid mass. If the patient survives, as is sometimes the case, for weeks or months, the clots become firmer and the pulsation may diminish or even disappear entirely. But even very shortly after the rupture the pulsation may be readily overlooked in the intensity of the other symptoms. Many of them present the features of the acute abdomen, and as already mentioned there are a number of recent cases in which the patients have been operated upon for this condition, usually with the diagnosis of appendicitis, without the slightest suspicion on the part of the surgeon that an aneurism was present.

Certain Special Points in Relation to Thoracic Aneurism.—Innominate or arch? The question is important with a view to surgical interference. The innominate is affected in many aneurisms of the arch, either uniformly dilated with it, or the orifice of the vessel is given off in the sac. The high position of the tumor, the presence of pulsation of the sternoclavicular joint without pulsation in the second and third right interspaces, the extension of a definite tumor above the sternal notch, and above all the information to be obtained by the *x*-rays, are the important points. In young persons with aortic insufficiency there may be a prominent tumor above the clavicle, due to dynamic dilatation of the arch and innominate. In the following case a sac of the arch in a peculiar position led to a mistake in diagnosis: In 1879 there was in the Montreal General Hospital a man, aged thirty-eight years, with a strong pulsation above the right stenoclavicular joint. On palpation the outlines of the tumor could be felt, with a smooth, rounded border just above and behind the joint. Vigorous lateral pulsation was felt with one finger in the sternal notch and the other at the outer border of the sternocleidomastoid muscles. There was flatness behind the inner end of the right clavicle. A loud, systolic murmur was heard, but he had no aortic insufficiency. There was slight paralysis of the right cord. The question arose as to the possibility of cure by distal ligature, as the aneurism was thought to be of the innominate. He refused operation, and died

[1] *Clinical Society's Transactions*, 1878, vol. xi, p. 123.
[2] *St. Bartholomew's Reports*, 1879, vol. xv, p. 75.

of pneumonia about four months later. At the postmortem a dilated aortic arch was found, and just before the innominate was given off there was a small aneurism the size of a walnut, conical in shape, which passed up by the side of this vessel, occupying a position immediately behind the sternoclavicular articulation.

The X-rays.—With a good apparatus in the hands of an expert the results are of extraordinary value. There is rarely difficulty in the diagnosis of the saccular aneurism, as the shadow pulsates and the rounded mass is readily differentiated. F. H. Baetjer, who had a very large experience with aneurism at the Johns Hopkins Hospital, classifies the positions as follows:

1. "Aneurism of the ascending portion of the aorta usually casts a shadow more to the right than to the left of the sternum, above the heart, and by localization would be found to be nearer the anterior than the posterior wall of the chest."

2. "Aneurism of the arch casts a shadow slightly to the left of the sternum, and this shadow extends well up into the neck, and by localization would be found nearer the anterior chest wall."

3. "Aneurism of the descending arch of the aorta casts a shadow to the left of the sternum, and by localization would be found nearer the posterior than the anterior chest wall."

In the diffuse aneurism with the arch uniformly dilatated a broad shadow extends along the sternum on both sides, and pulsation of the shadow may be seen and the shadow persists between pulsations. In the simple dynamic dilatation of the aorta, pulsation of the shadow is visible, but between the pulsations the shadow disappears, as the aorta contracts and its shadow lies within that cast by the sternum and the spine. In large aneurisms the depression of the heart and its somewhat transverse position are usually well seen. It is particularly in the group of aneurisms without physical signs that the *x*-ray examination is of the greatest possible value. We had at the Johns Hopkins Hospital a most interesting series of such cases, many of which have been reported by Baetjer. One in greatly impressed with the accurate localization of the tumor in some of these latent cases. A woman, aged twenty-three years, was admitted cyanosed and with urgent dyspnœa. There was evidently tracheal compression. After she was relieved by venesection a most careful examination of the chest could detect but one physical sign—less air entered the lower lobe of the left lung than the corresponding lobe of the right lung. The *x*-ray examination showed a small aneurism of the transverse arch; the position corresponded accurately with that as determined at the postmortem. Several of the latent cases presented only persistent pain. In skilful hands there is rarely much confusion between aneurism and tumor. Williams, the pioneer in radioscopic work in internal medicine in America, very fully sums up the position in the following words: "To make a definite diagnosis of aneurism by the usual physical examination we may be obliged to wait for the development of marked signs, and this delays treatment. On the other hand, if the physician begins treatment because the signs are

PLATE VII

Skiagram of an Aneurism of the Thoracic Aorta.

suspicious, he runs the risk of subjecting his patient to unnecessary regimen. The advantages of *x*-ray examination when compared with the usual physical examination are evident. A definite diagnosis can be made in most cases before there are physical signs. Treatment can, therefore, be begun at an earlier and more hopeful stage, can be planned more intelligently as the knowledge of the position and extent of the aneurism is more accurate, and its results can be better estimated because we can more accurately measure any change in size."

Prognosis.—In aneurism of the aorta the outlook is always grave, and yet a number of cases recover. The mode of cure has been spoken of. Lebert estimated that the period of the evolution of an aneurism was from six months to four years. In a great majority of all cases the fatal result occurs within two years from the onset of the symptoms. The most favorable is the saccular form projecting anteriorly or to the right, but it is not always easy to determine the exact shape, although now with the *x*-rays one can often get a very good idea of the form. Once an aortic aneurism is healed, the individual may live for many years. Under Dissecting Aneurism the case of a soldier who was invalided for aneurism after the Crimean War, in 1855, and who lived until 1881, was mentioned. Among favoring elements in the prognosis are: (1) Position and form of the sac. Moderate-sized, saccular aneurisms of the ascending arch, of the descending part, and of the abdominal aorta are more frequently seen obliterated than those springing from the transverse arch. (2) Early diagnosis and treatment. In the case of a young man who has had syphilis, specific treatment thoroughly carried out, in combination with absolute rest, gives at least a chance of cure. (3) In a few instances the sac projecting anteriorly has been permanently occluded as a result of operation. The San Francisco case operated upon by Rosenstern lived for many years. Even after a sac has perforated the chest wall, life may be prolonged. Jamieson reported the case of a man aged thirty-two years, who lived and worked for twelve years with an aneurism projecting through the chest wall. There are deceptive features in thoracic aneurism which must be taken into account in the prognosis. The pulsating tumor may diminish, may even disappear, and yet the sac may increase in another direction. In a case of this kind, which was seen with George Ross, of Montreal, the patient had been most faithful in carrying out a strict Tufnell treatment, and had taken potassium iodide in very large doses. The pulsation anteriorly had lessened remarkably, and it was thought that surely the aneurism was healing, but he died suddenly of rupture into the pleura, into which, it was found at postmortem, the sac had extended.

Death takes place usually from the rupture of the sac, sometimes from sudden paralysis of the heart, rarely from the effects of pressure or from gradual asthenia.

Treatment.—Necessarily in great part symptomatic, only in a few cases is a cure effected. In a case of thoracic or abdominal aneurism seen early the following plan of treatment may be carried out:

1. *Rest.*—By diminishing the vigor of the heart's action, and possibly

by diminishing the volume of the sac, there is often an extraordinary relief to the cough, the shortness of breath, and the pain. The rest should be complete, the patient remaining for from six to twelve weeks in the recumbent posture and making as few movements as possible. It is not an easy treatment to carry out. If the aneurism is large and has already eroded the chest wall, it is hardly worth while to insist upon prolonged rest. Between the recumbent posture and the erect with exercise the reduction of the number of pulsations per minute in the sac may be from twenty-five to thirty, so that in the course of the day there is a considerable saving of the strain upon its walls.

2. *Diet.*—The intake of solids and liquids may be reduced to a minimum. Tufnell's diet is as follows: "For breakfast, two ounces of bread and butter and two ounces of milk or tea; dinner, three ounces of mutton, three ounces of potatoes or bread, and four ounces of claret; supper, two ounces of bread and butter and two ounces of tea; total *per diem*, ten ounces of solid food and eight ounces of fluid, and no more." Only in early cases is it worth while to put the patient to the serious inconvenience of this diet.

3. To aid in the reduction of the blood pressure, and to increase the tendency to coagulation in the sac, small bleedings may be practised, five or six at intervals of a week, taking six to ten ounces of blood. This triple combination of rest, low diet, and bleeding is the Valsalva method, which was used with success by Albertini and other Italian physicians in the eighteenth century. Morgagni gives it succinctly: "When as much blood as was requisite was withdrawn (by repeated small bleedings), he (Valsalva) ordered a progressive diminution of food and drink until the quantity was reduced to a determined weight of aliment and water. Having so enfeebled the patient that he could scarcely raise his hand from bed, on which he was ordered to lie from the beginning, the quantity of aliment was cautiously increased." Morgagni remarks: "There are many persons to whom Valsalva's method of cure may appear more intolerable than the aneurism itself, especially at the only time when any treatment could avail. The inconvenience of the disease at that period is but slight and the danger is not imminent, etc."

4. *Iodide of Potassium.*—The value of this drug in aortic aneurism is undoubted. Formerly the favorable results were attributed to condensation of the sac by its action on the fibrous tissues and to the promotion of coagulation. A more rational view is that the luetic mesarteritis is directly influenced by it. It is remarkable with what promptness the pain is relieved in the syphilitic cases. Formerly we gave enormous doses, up to 200 and more grains three times a day, but of late years the writer has found that moderate doses are just as effective, and it is rarely necessary to give more than 25 to 30 grains (1.5 to 2 gm.) three times a day. When the syphilis has been recent mercurials may be given as well.

5. *Measures to Allay Pain.*—The iodide of potassium often gives relief. Local applications—belladonna plasters, an ice-bag, a hot poultice, or a hot-water bottle—are helpful, but in the majority of cases, when

the pain is due to pressure, morphine must be given. And in such a desperate malady it is well to give it early and freely.

6. Additional measures employed *to increase the coagulation of the blood.* To assist the low diet and rest and iodide of potassium in promoting the coagulability of the blood, calcium lactate may be given in from 15 to 20 grains (1 to 1.3 gm.) doses three times a day. Gelatin subcutaneously injected, 200 to 250 cc. of a 2 per cent. solution, was introduced by Lancereaux. The writer gave it a very thorough trial for several years, and the cases from his clinic have been reported by Futcher. In one or two instances it seemed to diminish the pain and lessen the size of the sac; but we did not get in any case the brilliant results which the distinguished author of this plan of treatment reports. Of 126 collected cases from the literature, benefit followed in 58 (v. Bottenstern).

Not in every case of thoracic or abdominal aneurism should a *cure* be attempted. A majority of the patients come under observation at a period when symptomatic treatment is alone possible. In what class of cases may a cure be expected? In the young syphilitic subject under thirty, in whom the diagnosis is made early, in cases in which the fluoroscope shows a small and sacculated aneurism, and in elderly persons, in whom, as postmortem experience teaches, the sac may spontaneously heal. When the sac is large, or if the fluoroscope shows a diffuse dilatation of the arch, it is best to allow the patient to continue his occupation, unless it is too arduous, and treat the symptoms as they rise.

What is to be done to relieve the frightful pressure *dyspnœa?* Patients are not infrequently brought to hospital cyanosed, gasping for breath and literally choking to death. As already stated, it is not always easy at first to make a diagnosis, but it is well to remember that in 9 out of 10 of such cases in adult males aneurism is the cause. Venesection from one or both arms to 25 or 30 ounces may give prompt relief. The removal of much smaller amounts may be effectual. It may be repeated several times in the course of a week. There are very few conditions in which free bleeding is so helpful. Morphine hypodermically should be given, unless there is an extreme degree of pulmonary infiltration, as shown by fine bubbling rales. In any case, if the patient is *in extremis* and suffering, it should be given. In the paroxysmal dyspnœa suggesting spasm of the larynx, due to irritation of the recurrent laryngeal nerves, the inhalation of chloroform may be tried; even if not immediately relieved, the comfort to the sufferer is very great. Should tracheotomy ever be performed in these cases? Theoretically, of course, with an aneurism or a tumor garroting the trachea at the bifurcation, it is useless, and yet it is often impossible to resist in the case of a poor fellow admitted choking and in a dying state. The writer has seen it done in a good many cases, never with permanent benefit, occasionally with temporary relief. In one case the woman's suffering was so frightful that after a preliminary tracheotomy Dr. Halsted attempted to reach the seat of compression by resecting the upper portion of the sternum, on the chance of giving freedom in this way and possibly of placing one of his rings

about the aorta above the sac, the position of which could be accurately defined with the fluoroscope. The patient died on the table in a paroxysm. In a case at the West London Hospital, under Seymour Taylor, tracheotomy gave immediate relief.

Surgical Treatment of Internal Aneurism.—Ligation of the aorta has been done ten or twelve times for aneurism of the abdominal aorta, always with fatal result. *Digital compression* has been tried in many cases. William Murray, of Newcastle-on-Tyne, cured a man aged twenty-six years, who had a pulsating tumor to the left of, and above the umbilicus. Between the sac and the free border of the rib there was room enough to permit one part of a tourniquet to press on the spine and control the pulsation. The patient was put under chloroform for two hours, during which time the pulsation was arrested. On removal of the pressure there was no effect. Three days later the pressure was again applied under anesthesia of five hours' duration. In the last hour the pulsation was no longer evident when the tourniquet was released, the extremities were cold, and the femorals could not be felt. The patient got perfectly well and lived six years, when another aneurism occurred at the cœliac axis.[1] A number of successful cases have been reported. When by digital compressions or a tourniquet the pulsation in the sac may be obliterated, this is the safest method. But it is not always satisfactory, and death has followed from peritonitis, obstruction of the bowels, and reduction of the pancreas to a pulp.

Insertion of Foreign Bodies in the Sac.—In 1864, C. H. Moore, of the Middlesex Hospital, attempted the cure of aneurism by the introduction of wire into the sac, believing that by it coagulation of the blood would be favored. He put 78 feet of fine wire into the sac of a thoracic aneurism. Death occurred on the fifth day. Many other substances have been used, catgut, horsehair, Florence silk, etc. It has not been a very successful method.

Electrolysis.—Corradi recommended the passage of an electrical current through the wire inserted into the sac, and this Moore-Corradi method is the one most frequently used.

In the hands of Finney and Hunner at the Johns Hopkins Hospital the technique has been much improved,[2] and the operation is one that may be performed with safety in suitable cases. Of 23 cases treated in this way, 17 thoracic and 6 abdominal, 4 were cured. Three cases were improved. In 10 cases death was probably hastened. Of my series of cases of aneurism of the abdominal artery, 7 were treated by the Moore-Corradi method, 2 were improved, and 1 was alive three and a half years after the operation. The sacculated tumor with small orifice is best adapted for this, and with the improved facility afforded by the *x*-rays in determining the position and shape of the aneurism the chief difficulty will be overcome in the selection of suitable cases.

[1] *Medico-Chirurgical Society's Transactions*, 1864; *Inductive Method in Medicine*, Murray, 1891, p. 120.

[2] *Johns Hopkins Bulletin*, 1900, vol. xi, p. 263.

Needling the Sac.—Macewen introduced the practice of needling the inner lining of the aneurism with a view of promoting thrombus formation. It has been successful in a few cases. The practice of injecting irritating liquids into the sac—iodine, tanning, perchloride of iron—has been given up.

For the statistics of the surgical treatment of the important recent series of cases of arterio-venous aneurism the reader is referred to W. F. Stephenson's *Report on the Surgical Cases in the South African War*, London, 1905, p. 223, and to the paper by Saigo in the *Deutsche Zeitschrift f. Chirurgie*, Band xxxv, on traumatic aneurism in the recent Russo-Japanese War.

CHAPTER XIII.

THROMBOSIS, EMBOLISM, AND PHLEBITIS.

By GEORGE BLUMER, M.D.

THROMBOSIS.

Thrombosis may be defined as "the formation of a solid mass or plug in the living heart or vessels from constituents of the blood" (Welch). The term thrombus is applied to the plug so formed.

Etiology.—Leaving aside the occasional cases of thrombosis associated with trauma, and assuming that morphological changes in the blood are not proved to have a direct bearing upon thrombosis, there are two causes of importance in the production of the process; namely, mechanical and chemical factors.

Inasmuch as our knowledge of the *mechanical* causes stands on a firmer footing than our knowledge of the chemical ones, these may be considered first. The most important of these factors is the slowing of the circulation in the heart or the vessel in which the thrombus forms, and the formation, in connection with the slowed current, of whorls or eddies. There is abundant evidence, both clinical and experimental, which shows that thrombosis is most likely to occur in those portions of the circulation where the physical conditions above mentioned occur. Roughening of the lining membrane of the vessels as a cause of thrombosis cannot be considered as a purely mechanical factor, for, while it may be productive of slowing of the blood stream, the setting free of thromboplastic substances plays an important part in this form of mechanical change. In connection with any mechanical factor, it must be borne in mind that slowing of the blood stream in itself is not sufficient to lead to thrombosis, and that the chemical factors also must be present.

The *chemical* factors have to do with two different processes: alteration in the chemistry of coagulation of the blood and the action of agglutinating substances. The part played by alterations in the physiology of coagulation has generally been held to be an important one, but in recent years there has been a decided tendency to decry its importance. The exact mechanism of normal coagulation is still under discussion, though the work of Morawitz, of Loeb, and of Howell and his pupils has led to suggestive hypotheses. It is generally agreed that the normal blood contains prothrombin, calcium salts, antithrombin, and fibrinogen, and that practically all tissues contain thromboplastin. The last-named substance is also present in the blood platelets, at any rate after they have undergone disintegration. Morawitz's theory of the process of coagulation leaves out of account the presence of antithrombin, and assumes that thromboplastin acts as a ferment leading to the formation of fibrin from the union of prothrombin and fibrinogen in the presence of calcium. By the researches of Howell and his pupils the weakness of this hypothesis

is made clear, and an alternate theory—that the thromboplastic substances neutralize the antithrombin, thus allowing the union of prothrombin and fibrinogen—is substituted. Theoretically, if we assume that Howell's hypothesis is correct, a deficiency in antithrombin would be the most likely predisposing factor in the production of human thrombosis, and his researches on the blood of patients with thrombosis seem to prove this to be the case. Inasmuch as this substance is, in all probability, formed in the liver, future students may perhaps look to changes in this organ as accompaniments of a tendency to produce thrombi.

The rôle of *agglutination* in the production of thrombosis appears to be increasing in importance as that of coagulation appears to be decreasing. It is probable that the relation of infection to thrombosis, at least in some instances, has to do with the formation of agglutinins as the result of bacterial infection, possibly acting indirectly through tissue destruction. This does not exclude the action of infection in other ways, such as by the production of injuries to the lining of the vessels. The experimental work of Pratt, who showed that in the frog, the rabbit and the dog the youngest thrombi are composed of agglutinated platelets and red blood corpuscles and do not contain fibrin, is of great importance in its suggestion that agglutination plays a much more important part in the development of most thrombi than has usually been assumed. It has been known for years, as the result of the work of Hueter, von Recklinghausen, Welch, and others, that a good many thrombi, even quite large ones, are histologically agglutination rather than coagulation thrombi. The assumed relationship between internal secretion and thrombosis may be dismissed with the Scotch verdict, "not proven."

Any consideration of the etiology of thrombosis would be incomplete without mention of the part played by *racial* and *family* peculiarities. Within recent years the very strong tendency of the Jewish race to thrombo-angeitis has been well demonstrated. Aside from this racial tendency to thrombosis, there are undoubtedly certain families in which a tendency to the development of thrombosis exists. Such families may be described as thrombophilic in contrast to those hemophilic families in which a tendency to bleed is such a pronounced feature. It seems likely that in time it will be shown that in such families changes either in the normal coagulability or in the agglutinability of the blood exist.

Etiological Relationship of Various Diseases to Thrombosis.—It is well known that individuals suffering from certain diseases are likely to develop thrombosis, while those suffering from other diseases seldom acquire this complication. A knowledge of the disease associations of thrombosis is therefore desirable.

Typhoid Fever.—Cardiac and arterial thrombi are seldom met with in the course of typhoid fever. Arterial thrombosis occurs in about 0.35 per cent. of all cases, according to Thayer. The lesion generally attacks the lower extremity and, when complete, usually results in gangrene. In a fair number of cases the thrombus does not completely occlude the vessel and perfect recovery occurs. In contrast to venous thrombosis in typhoid, the two sides are equally affected. The visceral arteries, especially the middle cerebral, are not infrequently involved. The complication usually occurs during the febrile period.

Venous thrombosis occurs, according to Thayer, in two and one-half per cent. of all cases of typhoid fever. In the great majority of instances the veins of the lower extremity are involved and the left side much more frequently than the right. The popliteal, iliac, and calf veins are stated to be involved only one-fourth as frequently as the femoral veins. This statement is, we think, open to doubt, as many femoral thromboses have their beginnings in involvement of the deeper veins, especially those of the calf.

Pneumonia.—Cardiac and *arterial* thrombosis is rare in pneumonia. Most of the cardiac thrombi which are described in the literature as occurring in this disease are postmortem, the mistake being due to the unusually firm postmortem clots found in this disease. Thrombosis of the peripheral arteries is much less common than embolism and is usually associated with great feebleness of the circulation. The occurrence of *venous* thrombosis is probably less infrequent than the literature would indicate. The small number of cases which Steiner was able to collect probably gives an entirely false impression of the frequency of the complication. In the past two years the writer has observed three cases. The thrombosis usually involves the lower extremities, especially the femoral vein, the left side being much more frequently attacked than the right.

Influenza.—Cardiac thrombi of a marantic nature have occasionally been reported and a few instances of globular thrombi are on record. Thrombosis in association with an influenzal endocarditis has been reported a number of times in recent years. *Arterial* thrombosis, while more common in influenza than in most of the infectious diseases, is comparatively rare. According to the German statistics, it occurs in only 0.005 per cent. of all cases. The vessels of the lower extremities are attacked in the great majority of instances. The figures, both of Welch and of the German Committee, show that the popliteal artery is most frequently involved; next, the femoral; and less frequently, the iliac, axillary, and brachial. The cerebral and occasionally the pulmonary arteries are thrombosed in this disease.

Venous thrombosis is comparatively frequent, usually occurring either late in the attack or during convalescence. The veins of the lower extremities are usually involved, though the brachial and axillary seem to be more frequently thrombosed than in other infections. The severity of the disease seems to have little bearing upon the likelihood of thrombosis. There are too few cases on record to satisfactorily substantiate Leichtenstern's view that venous thrombosis in influenza is more apt to lead to gangrene than venous thrombosis associated with other diseases.

Postoperative Thrombosis.—The association of thrombosis with operative procedures, particularly with abdominal operations, has been a subject of much comment in recent years. Beckman's figures from the Mayo Clinic, based upon 3657 consecutive cases, show 0.0046 per cent. with thrombosis. Certain abdominal operations seem more likely to give rise to this complication than others, and operations for uterine myomata and appendicitis seem especially prone to be followed by thrombosis. In many instances the complication occurs in cases which are apparently entirely free from sepsis. The condition usually involves the veins of

the lower extremities, especially the left femoral vein, and this entirely independent of the site of incision and operation. Much discussion regarding the etiology of this form of thrombosis has resulted in a wide diversity of opinion. Some writers, as Clark, incline to place the chief blame on mechanical conditions, such as trauma to small vessels during operation. They believe that the involvement of the femoral is secondary to a spread from these smaller tributaries. Other writers hold the view that phlebitis due to an attenuated sepsis is at the bottom of most cases and this view is substantiated in some cases, at any rate, both by the febrile course of the complication and by the fact that bacteria have occasionally been isolated from such thrombi. Their frequent occurrence in connection with the removal of the uterus and ovaries has led to the hypothesis that the internal secretions of the female sexual organs exert some influence on the process. The careful review of Schickele indicates that there are no solid grounds for such a belief. There is a good deal of evidence which tends to show that the complication is less frequent in those patients who are allowed to sit up and get out of bed at a comparatively early period after operations. The subject is still unsettled and it is probable that different factors are of importance in different cases.

Rheumatic Fever.—All forms of thrombosis are exceedingly rare in this disease. Cardiac thrombosis, aside from that occurring with a complicating endocarditis and arterial thrombosis, is almost unknown. Venous thrombosis is of rare occurrence and when present usually involves the veins of the lower extremities and is associated with a definite phlebitis.

Tuberculosis.—*Cardiac* thrombi occur, according to Ruge and Hierokles, in but two-tenths of 1 per cent. of patients dying of pulmonary tuberculosis. *Arterial* thrombi are also very uncommon, though occasionally small parietal thrombi form on the intima of the vessel in acute miliary tuberculosis. *Venous* thrombosis occurs in something over 1 per cent. of all patients with chronic pulmonary tuberculosis and may be symptomatically latent. The process may occur early but is most common during the terminal stages. Women are said to be more subject to it but the figures are too small to prove this statement satisfactorily. As in other forms of venous thrombosis, the peripheral veins of the lower extremities are most frequently involved, though the veins of the internal organs and of the arms are occasionally affected. The enfeebled circulation which accompanies the terminal stages of chronic tuberculosis and the frequency of terminal infections are probably the important factors.

Gonorrhœa.—All forms of thrombosis are rare in gonorrhœa though venous thrombosis is much more common than the cardiac or arterial forms. When it occurs, it affects men in over two-thirds of the cases. It generally appears in the subacute stages of a first attack and involves the veins of the lower extremities, particularly the internal saphenous. The cerebral sinuses and veins of the upper extremities are occasionally involved, as are the veins of the genitalia. Gonorrhœal arthritis is a not infrequent accompaniment of thrombosis, suggesting that the thrombus formation is a manifestation of a general gonococcus septicemia.

Syphilis.—*Cardiac* and *arterial* thrombosis are both very rare during the course of syphilis, if we except the thrombosis occurring in connection with syphilitic aortitis accompanied by aneurism. Of the peripheral vessels, the veins are the ones most frequently attacked by the luetic infection, and thrombosis usually occurs in connection with phlebitis. The process may occur at any time but is most common in the secondary stage. It is much more common in males than in females and seems most likely to occur in those whose occupation keeps them on their feet. The veins of the lower extremities are especially apt to be involved, and, as in gonorrhœa, the internal saphenous vein is more frequently involved than any other. Multiplicity of involvement is common, as are successive exacerbations of the process in the same vein. The symptoms come on insidiously in many instances. There is a rare form of the disease known as syphilitic erythema nodosum or nodular thrombophlebitis, in which red or violet nodosities resembling those of erythema nodosum appear along the course of the veins, usually those of the lower extremities or the corpus cavernosum.

Chlorosis.—Cardiac and arterial thrombosis in chlorosis is very unusual. *Venous* thrombosis, on the other hand, is a relatively common complication. Leichtenstern estimates that thrombosis occurs in about 1 per cent. of chlorotics. His figures show that the veins of the lower extremities are involved almost exclusively, if the peripheral vessels only are taken into account. Thrombosis of the cerebral sinuses is reported hardly less frequently, however, but the published figures give an entirely erroneous impression regarding the frequency of sinus thrombosis, which is rare. In the lower extremities the smaller veins, especially the calf veins, are frequently involved, and for this reason the process is much more likely to be overlooked than when the femoral or internal saphenous are occluded. The left leg is more frequently affected than the right, and bilateral involvement is exceedingly common. The percentage of emboli resulting from peripheral thrombi in chlorosis is very high compared to thrombosis associated with other conditions. Welch states that there is embolism in 25 per cent. of the cases. This renders the prognosis of chlorotic thrombosis graver than that of any other form with the exception of puerperal thrombosis.

Miscellaneous Parasitic Diseases and in Cachexia.—Thrombosis has occasionally been described in a variety of infections other than those considered. In dysentery both arterial and venous thrombosis is occasionally met with, also in chronic diarrhœa, especially in feeble infants and old people. In Asiatic cholera, diphtheria, erysipelas, chronic suppuration, plague, measles, peritonitis, dental caries, nephritis, and scarlet fever, occasional instances of thrombosis are reported. Typhus fever is the infectious disease most commonly associated with arterial thrombosis but this appears to hardly ever occur in the attentuated form present in this country. Thrombosis in malaria is a rare occurrence, many of the cases reported under this head being doubtful. In the cachexia associated with malignant neoplasms and in anemias of the severer grades, thrombosis is not unusual. Where predisposition exists, thrombosis may even result from the pressure of the cuff used

in determining blood pressure. The cachectic thromboses are associated with a variety of causes, especially degenerative changes in the bloodvessels, enfeeblement of the circulation, and terminal infections.

Cardiac Disease.—The thrombi which occur in the heart itself are practically never recognized clinically, but arterial thrombosis may occur, especially associated with endocarditis, and is not difficult of recognition. In decompensation, arterial thrombosis is hardly ever encountered, while peripheral venous thrombosis is a not infrequent complication. The peripheral *venous* thrombosis of decompensated heart disease differs mainly from that in other conditions in the great preponderance of the involvement of the vessels of the upper extremities. The complication attacks males more often than females and occurs most frequently in patients with mitral valve disease between the ages of fifteen and thirty. It is common for more than one vessel to be involved, and the most usual combination is a continuous thrombosis of the innominate vein, the internal and external jugular veins, and the subclavian and axillary veins. The left side is much more frequently attacked than the right, partly because there is frequently a developmental error on that side near the junction of the internal jugular and subclavians, and partly because the pressure of the dilated left auricle comes into play. There is also an unusual opportunity for the formation of eddies in the jugular bulb. On account of the fact that these patients are generally in the last stages of decompensation, and frequently have also a terminal infection, the outcome is usually fatal. However, I have seen two cases in which compensation was reëstablished after the development of a venous thrombosis.

Gout.—Two types of thrombophlebitis have been described in connection with gout. In one, there is no question of the relationship as the complication occurs during the attack, probably as the result of the extension of the inflammatory process, the veins in the neighborhood of the inflamed joint becoming thrombosed. The second type was stated by Paget to occur in persons of marked gouty constitution or with gouty inheritance. Inasmuch as similar cases have been described without any history of gout, we may be pardoned if we are skeptical concerning the gouty nature of many of them, especially when we remember the loose way in which the term gout is used by English writers. It is probably better to describe these cases under the heading of *idiopathic recurrent thrombophlebitis* or *phlebitis migrans*. There is a strong hereditary tendency in many of these cases, which resemble, in their tendency to recurring attacks, certain cases of syphilitic phlebitis and the condition of thromboangeitis obliterans. The disease usually attacks the superficial veins of the lower limbs, involving short segments of the vessels, recurring frequently without obvious cause, and producing comparatively little discomfort in the way of local or general reaction. As in other forms of thrombosis, the left side is more frequently involved than the right, and the lower more frequently than the upper extremities. There is disagreement regarding the danger of secondary embolism, Briggs claiming that it is not great, while Daguillon lays stress upon its importance.

Primary Infective Thrombosis.—There are a few reported cases of patients presenting the clinical picture of general sepsis accompanied by widespread thrombosis, both in the veins and arteries, but usually predominating in one group of vessels. The most striking clinical feature in some of these patients is the absence of symptoms and physical signs at all comparable in severity to the extent of the vascular lesions. In the patients of Dowse and Osler, this latency of symptoms was not very marked as the peripheral vessels were the ones mainly involved. In the very remarkable cases of Eichhorst, the lack of marked symptoms referable to the internal organs, in spite of widespread thrombosis of their vessels, was a striking feature. Eichhorst's conception of the condition is that it is a sepsis in which, as the result of bacterial infection through the vasa vasorum, localized areas of arteritis with thrombus formation are produced. It is possible, however, that in some instances the infection occurs through the intima by way of the circulating blood.

Special Pathology.—Structure of Thrombi.—In the common varieties of thrombi the plug is constituted of the formed elements of the blood, the red and white corpuscles, and the platelets, plus fibrin. The main factor which decides the appearance and structure of such thrombi is the physical condition of the blood stream at the time the thrombosis occurs. If the process involves stagnating blood, a red or cruor thrombus occurs. If the blood is still circulating, a white thrombus results. Mixed thrombi occur when, during the formation of a white thrombus, the circulation is markedly impeded or stopped, so that portions of the plug are composed of stagnating or almost stagnating blood, or they may occur from fissuring of a white thrombus with a formation of red thrombi in the fissures.

Thrombi are apt to be confounded with postmortem clots, the distinction between the two being, however, usually not very difficult. The postmortem clot is common in the cavities of the right side of the heart, in the cerebral sinuses, and in the veins. It may be entirely red, or, what is common in the heart especially, mixed red and yellow, the yellow portion often having a striking resemblance to chicken fat. In the heart such clots often penetrate between the columnæ carneæ, giving a false impression of being adherent, but are easily detached and with very little experience can be distinguished from true mixed or white thrombi which are usually so firmly adherent that they cannot be removed without tearing. In the vessels also, postmortem clots which are partly yellow and partly red may be formed and may be taken for mixed thrombi. In this instance the red portion of the clot is the dependent portion, and here again the clot, as distinguished from the true thrombus, is easily detached from the vessel wall. The grayish color and opaque appearance of the white thrombus is usually quite different from the yellowish color and semitransparent appearance of the postmortem clot. The consistency of the two is different, the postmortem clot being elastic and homogeneous, the thrombus granular and rather friable. The peculiar ridging of the surface of certain thrombi is never seen in postmortem clots. These remarks refer particularly to the white or mixed thrombi. Red thrombi when recently formed may be much more difficult to distinguish from postmortem clots. Usually in red thrombi the deposition somewhere on the

surface of a white film composed of leukocytes, platelets, and fibrin serves as a point of differentiation. In older red thrombi the marked adherence to the heart or vessel wall and the granular consistency render differentiation easy.

Microscopically red and white thrombi differ considerably in structure. Red thrombi are composed of the formed elements of the blood, in approximately their normal proportions, traversed by fine strands of fibrin. White thrombi are made up of a framework of granular material composed of fused blood platelets, in the meshes of which are red and white corpuscles and fibrin in proportions which vary according to the rapidity of the blood stream at the point of thrombus formation. Leukocytes are usually present in good numbers, especially along the edges of the platelet network, and fibrin threads occur mainly among the leukocytes. Red corpuscles are not numerous if the circulation was rapid when the thrombus formed, but may be present in large numbers if the circulation was feeble. It is on the surface of white or mixed thrombi that the transverse ridges, described especially by Zahn, may be seen. They run at right angles to the long axis of the vessel, lie roughly parallel to one another, and may be united by fine oblique striations. The appearance is due to a physical action of the circulating blood upon the viscous surface of the thrombus similar to that produced on the sand of river banks or the seashore by the waves.

Method of Formation of Thrombi.[1]—Different ideas have been held at various times as to the nature of thrombus formation. Briefly stated, the two main views have been: (1) That it is merely a process of coagulation. (2) That the essential process is an agglutination of the blood platelets with which coagulation is associated as a secondary process. The idea that thrombosis is coagulation pure and simple has now been abandoned by most pathologists; at any rate, so far as the formation of the more common white or mixed thrombi is concerned. The generally accepted view as to the formation of such thrombi based upon experimental work and the study of human lesions, indicates that the first step in the thrombus formation is the accumulation of blood platelets at the point where the lesion occurs. The observations of Pratt show that red blood corpuscles are also present in the early stages. This is followed by the transformation of the platelets into a sticky mass (viscous metamorphosis) which causes them to adhere to one another and to the vessel wall. Later polynuclear leukocytes accumulate in the interstices of the mass, and fibrin appears. Red corpuscles are present in numbers varying inversely to the rapidity of the blood current at the site of thrombus formation. The latter part of the process is believed to involve the ordinary changes which accompany coagulation.

The manner of formation of the agglutination thrombi composed of red blood corpuscles, which occur in connection with certain infections and intoxications, has been described by Flexner. The red corpuscles fuse as a result of the action of the poison into a dark, soft, conglutinated clot, the fluid portions of the blood being laked in appearance. Sections

[1] L. Loeb, *Virchows Archiv*, 1906, vol. clxxxv.

of experimental clots produced by the intravenous injection of ether, show agglutination of some of the red blood corpuscles, others appearing as shadows. Fibrin is not present in these experimental clots. In man such agglutination thrombi are made up of conglutinated masses of red cells with a few leukocytes, usually along the walls of the vessels, and but little fibrin. There seems now no doubt that in the later stages of such thrombi, transformation of the fused mass occurs, and the appearance is then that of the so-called hyaline thrombi.

Accepting Welch's definition of a thrombus as a plug formed during life from constituents of the blood, we must recognize two other varieties of thrombi which occur occasionally, viz., leukocyte thrombi and fibrin thrombi. Welch expresses the opinion that the formation of ordinary white thrombi from leukocytes, if it occurs, must be a rare event. In connection with local inflammatory lesions, however, a plugging of the regional vessels with leukocytes is not uncommon. Thrombi composed of fibrin from the beginning, as distinguished from old thrombi which have undergone fibrinous transformation, occur merely in small vessels and are devoid of clinical interest; they at times undergo transformation into hyaline material, constituting one variety of hyaline thrombi.

Growth in Thrombi.—Most vascular thrombi when they originate lie along one side of the vessel, constituting mural or parietal thrombi. In the cavities of the heart parietal thrombi are the rule, and are usually in the form of rounded or flattened masses projecting into one of the heart cavities. The auricular appendage may be completely filled with a thrombus mass, and a polypoid continuation into the auricular cavity is not uncommon. When, as occasionally happens, a thrombus becomes free in the auricle it may assume a globular form, and then constitutes a so-called ball thrombus. The vascular thrombus does not as a rule remain parietal, but ultimately fills the vessel, occluding the lumen (occluding or obstructing thrombus). It then usually extends, commonly in the direction of the blood stream, occasionally in an opposite direction. As a rule the extension ceases when the first branch of the vessel capable of reëstablishing the circulation is encountered; but this is not always the case, and thrombi may extend into the branches or may be continued on one wall of the vessel beyond the branch as parietal thrombi. When prolongation of the thrombus occurs, the extended portion is often much less adherent to the vessel wall than the original thrombus, and the terminal end of the growing thrombus is usually cone-shaped and entirely free in the blood stream. A marked extension of the thrombus seems more apt to occur in veins without valves. Infective thrombi are more liable to extend widely than aseptic ones.

Secondary Changes in Thrombi.—The most important of these is the process of organization which is essentially the same in all forms of thrombi. The active participants in the organization are the endothelial cells lining the vessel or heart, the connective-tissue cells of the cardiac or vascular wall, and the vasa vasorum. The process is often preceded and usually accompanied by degenerative changes in the thrombus, transformation of the platelet masses into a granular material, degeneration

of the leukocytes, decolorization and disintegration of the red corpuscles with hematoidin formation, increase in and coarsening of the fibrin strands, and more or less retraction and fissuring of the thrombus mass. In the actual process of organization the thrombus plays a passive part, acting for the time as a temporary scaffolding for the advancing vessels and connective-tissue cells, ultimately being removed, mainly by phagocytosis. The process consists in the vascularization of the clot by newly formed vessels which are pushed in as sprouting processes from the preexisting vasa vasorum, and which are accompanied by newly formed connective-tissue cells originating either from those preëxisting in the vessel wall or from the actively dividing endothelial cells of the intima. These proliferated intimal cells coat over the surface of the thrombus which is exposed to the blood stream, penetrating into the crevices and crannies formed by the retraction or fissuring of the clot. According to some observers newly formed vessels may also originate from the endothelial cells. The process results in replacing the thrombus by connective tissue, at first vascular and made up of an embryonic type of cell, later becoming fibrous and poor in vessels like cicatricial tissue. The ultimate result so far as the vessel is concerned may be a complete plugging with transformation of the thrombosed area into a fibrous cord, or more commonly a partial or even complete restoration of the circulation, either as a result of retraction of the organized thrombus or the formation through it of a series of blood channels uniting the circulation on either side. Occasionally a complete disappearance of the organized thrombus occurs, or it is represented by a few fine, thread-like adhesions which in no way interfere with the circulation.

The rapidity with which organization of the thrombus takes place is a matter of considerable importance, as the danger from secondary embolism gradually decreases as organization progresses. There are, of course, great individual differences in the capability of repair. In favorable cases organization may be well under way within a week. Certain factors may delay organization, such as infection, and disease of the heart or vessel wall. The importance of the latter factor can be realized when it is remembered that the process of organization proceeds from the tissues of the cardiac or vascular parietes. Under certain circumstances salts of lime are deposited in thrombi, more especially in venous thrombi. Rarely the calcified thrombus in its original form is transformed into a stony cylinder; more commonly calcified thrombi are in the form of spherical calcific nodules with smooth surfaces lying in the vein or artery almost free from attachment, and constituting phleboliths or arterioliths. The vein-stones are much the more common, look like small seed pearls, and are most often met with in varicose veins, in the veins of the spleen, and in the smaller pelvic veins, especially those about the base of the bladder.

Secondary degenerative changes in thrombi in the form of liquefaction or softening are of great practical importance on account of the increased danger from secondary embolism associated with them. Two forms of softening are generally recognized, the bland and the infective, the latter form being again subdivided into purulent and putrid softening.

This subdivision is based on the assumption that certain of the softened thrombi, *i. e.*, those classed as bland, are bacteriologically sterile, while the others are infected. The work of Harris and Longcope and Widal's researches on puerperal thrombosis have shown that bacteria are present in quite a large percentage of apparently bland thrombi, and this is often true even when no softening is present. Whether the softening of bland thrombi is due to infection is still an open question. From a clinical standpoint there is no question that emboli originating from softened thrombi do not all give rise to similar results, those from bland emboli causing a temporary febrile reaction and being comparatively harmless, while those from septic thrombi cause serious metastatic inflammations. It is possible that the bland softening is the result of an attenuated form of infection, although the fact that the escape of softened material into the circulation causes febrile reaction is not necessarily evidence that infection is present. It is known that thrombi contain constituents originating from the blood itself which are capable of producing fever when introduced into the circulation. Of the definitely infective thrombi, the putrid differ from the purulent in that they are due to bacteria of putrefaction as distinguished from the ordinary pathogenic cocci.

Puriform softening is most common in cardiac thrombi, but may result in those occurring in peripheral vessels. In the so-called bland softening the liquefied material has to the naked eye the appearance of more or less blood-stained pus. The microscope shows that the puriform material is made up of the debris of the constituent elements of the clot, granular and fatty particles, blood pigment, crystals of fatty acid, and more or less degenerated red and white blood corpuscles. In the infective thrombi the softened area has the appearance of true pus and contains under the microscope numbers of polynuclear leukocytes and bacteria. In putrid softening the thrombus is of a greenish or brownish color, and the liquefied area has an offensive odor similar to that encountered elsewhere in association with gangrenous processes.

Localization of Thrombi.—*Cardiac Thrombi.*—Two types of cardiac thrombi are to be observed, the mycotic thrombi, usually of small size, associated with endocarditis, and the larger thrombus masses found in the cavities of the heart in connection with conditions of an infectious or cachectic nature or associated with enfeeblement of the circulation. The mycotic thrombi being directly due to endocarditis, usually occur on the valves, but are occasionally mural. The second type of thrombi, which occur especially in chronic heart disease with failure of compensation, are met with in those situations where the circulation is slowest and where the physical conditions favor the formation of eddies. Such conditions are found especially in the auricular appendages and in the apices of the ventricles between the columnæ carneæ. The peculiar cardiac thrombi known as ball thrombi, almost invariably occurring in the left auricle in association with mitral stenosis, are due to the detachment of portions of mural thrombi which become moulded to a spherical shape through accretion and constant rotation in the auricular cavity. They are of pathological rather than clinical significance, as are the curious pedunculated cardiac polyps which usually spring from the

septum of the left auricle. Some of these are undoubtedly true organized thrombi; others are probably the result of intramural hemorrhage or are varicosities of the veins of the septum.

Arterial thrombi, commonly associated with chronic arterial disease or acute infectious arteritis, may occasionally accompany debilitating diseases or be due to trauma. They occur most frequently in the arteries of the extremities, particularly those of the legs, and involve the two sides of the body with almost equal frequency. The visceral arteries, especially those of the lungs, brain, heart, and intestines, are not infrequently involved, and sometimes main trunks like the aorta become thrombosed.

Venous thrombosis is by far the most frequent variety, as the mechanical and chemical conditions favoring thrombus formation are most frequently met with in the venous circulation. These conditions have been summarized by Welch as "the slower mean speed of the blood in veins than in arteries; the low blood pressure; the flow from smaller into larger channels; the absence of pulsation; the presence of valves; fixation of the venous wall in certain situations to fasciæ and bone; the existence in some places of wide sinuses and ampullar dilatations; the agency of certain subsidiary forces, such as muscular contractions and movements of the limbs, in assisting the flow in the veins; the composition of venous blood, particularly the rich content of CO_2, and perhaps the functions of the capillaries and small veins in the production and absorption of lymph."

Venous thrombi are found with the greatest frequency in the veins of the lower extremities, both superficial and deep, in the small pelvic veins, and in the cerebral sinuses. Thrombi in the veins of the arms are met with, and thrombi in the pulmonary veins are occasionally described. The venæ cavæ are, as a rule, only involved secondarily by the propagation of thrombi into them from their branches. A striking peculiarity of venous thrombosis is the marked tendency, both in the upper and lower extremities, to the involvement of the veins of the left side. This peculiarity is probably due to a variety of factors. The causes generally adduced in connection with the lower extremity have been the greater length and obliquity of the left common iliac vein, its situation beneath the right common iliac artery, and the exposure of the vein on this side to pressure from the distended rectum or sigmoid flexure. The recent researches of McMurrich[1] indicate that there is another important factor. This observer found in 10 out of 31 cadavers a localized adherence of the anterior and posterior walls of the common iliac vein just below its termination in the inferior vena cava. In 9 of 10 cases it occurred on the left side. McMurrich thinks it due to a developmental error. In like manner Hanot and Parmentier ascribe the frequency of left-sided thrombosis in the veins of the upper extremities to an interference with the return flow of blood resulting from the greater length and obliquity of the left innominate vein. In the upper extremity Hirschlaff has described developmental errors in connection with the valves near the junction of the internal jugular and subclavian veins

[1] *Brit. Med. Jour.*, 1906, ii, 1699.

analogous to those described by McMurrich in connection with the iliac veins, and, like them, much more frequent on the left side. *Capillary thrombosis* is of pathological significance only.

Local Effects of Thrombosis.—These depend mainly upon the degree in which the circulation is obstructed by the thrombus. In cardiac thrombosis and in thrombosis occurring in saccular aneurisms there is usually no marked disturbance of the circulation, and there may be little or none from parietal thrombi in vessels, provided the vessel is a large one and the thrombus small. In the great majority of arterial and venous thrombi there is serious interference with the circulation, and the result depends mainly upon two factors; the rapidity with which the vessel is closed, and the number of collaterals entering the area whose nutrition is cut off. In the case of peripheral vessels the rapidity of closure is the more important factor, as the vessels are usually well supplied with collaterals and there is free anastomosis. In the case of internal organs the character of the circulation is more important, for some organs have a terminal circulation in the anatomical sense and in others the amount of anastomosis is so slight that there is practically no chance for the formation of a collateral circulation. The gradual obliteration of an artery or vein by thrombosis is usually devoid of any result save the gradual development of a collateral circulation, although in some instances it may result in effects similar to those produced by a sudden stoppage of the circulation. The changes occurring from sudden stoppage of arterial blood supply from thrombosis are the same as those produced by embolism, and are so much more frequently the result of the latter complication that they are best considered under that head. Where obliteration of a vein of any size occurs suddenly, the most striking change is a venous or passive congestion followed by the escape of the blood serum into the tissues or the cavities of the body. There are records of rare instances in which thrombosis of the large venous trunks has been followed by gangrene, usually in patients the subjects of uncompensated cardiac disease with extreme feebleness of the circulation. In patients with thrombophlebitis, besides the purely mechanical effects of stoppage of the circulation, the local evidences of inflammation occur, with the usual clinical picture. In some instances, where the infection is intense, actual abscess formation about the thrombosed vein results. This is rather unusual in connection with the peripheral vessels, but is common enough in some situations, as in the branches of the portal vein.

Symptoms.—These will depend to some extent on the same factors which influence the effects of the process on the tissues, viz., the rapidity with which the circulation is cut off and the extent of the collateral circulation in the affected tissue. Certain local peculiarities in the vascularization of organs and in the sensitiveness of their cells to interference with the blood supply are also factors in causing variation in the symptoms. There is a certain percentage of thrombi in the peripheral vessels associated with gradual occlusion of the lumen which produce no symptoms whatever, and thrombi in the vessels of the internal organs are frequently latent or give rise to no clinical signs which permit of a diagnosis. Von Schrötter divides the symptoms of thrombosis into those which are

directly due to the formation of the thrombus and those which result from its effect on the blood supply. Of the former group *pain* is the most prominent, of the latter *œdema* or fluid in the cavities of the body. General symptoms, such as febrile reaction and quickened pulse, are also common. The symptoms of thrombosis vary so much according to the situation that it is necessary to consider the more prominent forms in detail.

Peripheral Venous Thrombosis.—This is the most common variety, and as the femoral vein is the most frequent site of the process, thrombosis of this vessel will be described. Premonitory symptoms and signs may occur many days before a discoverable thrombosis in some instances. As Conner has pointed out, these are usually pulmonary, and due to the lodgement of small emboli. The patient is apt to complain of sudden pain in the side with dyspnœa and cyanosis. Cough is at times present, and may be accompanied by bloody sputum. The temperature is little if at all affected. The signs vary from those of slight localized pleurisy to those of a fairly extensive plastic effusion, or localized consolidation of the lung may occur. In some instances chills may occur prior to the development of thrombi. The so-called "kletter puls" (climbing pulse) of Mahler has been shown to be unreliable as a premonitory sign, and Michaelis' premonitory period of subnormal temperature is also of doubtful value.

In a typical case both general and local symptoms are present. The general symptoms often precede the local ones, and the onset of the attack is at times a definite *rigor*. More commonly there are chilly sensations followed by fever and perhaps sweating, and an increase in the the rapidity of the heart's action. The *fever* in patients with bland thrombi is not usually high, 101° to 102° F., in an average case; in infective thrombosis it may be much higher, 104° or 105° F. Sweating is a rather common accompaniment of the fever, but is not always present. Examination of the blood at the onset of the thrombosis will often show a pure *leukocytosis*, although in diseases like typhoid fever, in which a leukopenia is the rule, the rise in the number of leukocytes may be slight or lacking. Not infrequently these general symptoms precede the local symptoms by several days.

The most prominent local symptom at the onset of thrombosis is *pain*. In femoral thrombosis this often appears first in the calf, although it may be present from the beginning at the site of thrombus formation. The pain is often intermittent at first, but gradually becomes a constant feature. It may not be very severe, but may be intense, and is described sometimes as burning or boring, sometimes as cramp-like. At first localized, it usually becomes more general as the disease progresses. Frequently the patient complains of a feeling of tension and weight in the limb. The pain is associated with tenderness of the affected member, most marked along the course of the thrombosed vessel, which can often be rolled under the fingers as a firm, sensitive cord. In spare individuals with thrombosis of superficial veins the course of the vessel may be traceable as a dull, red line on the overlying skin, usually rather wider than the diameter of the vein. Disturbances of sensation are uncommon,

aside from feelings of numbness and formication. In some patients, however, there may be intense neuralgic pains, especially in the domain of the sciatic nerve, and these are apparently due in some instances to a definite neuritis. Disturbance of motion is usually present, due to the natural tendency of the patient to immobilize the limb.

Œdema is the second prominent local symptom. Like the pain, it may appear first in the region of the calf and gradually extend upward, but in patients in whom infective thrombosis is present and in whom inflammatory œdema predominates, it may begin about the site of thrombosis and extend toward the periphery. The degree of œdema varies considerably; it may be very slight, but in well-marked femoral thrombosis is generally a prominent feature. Its character varies to some extent with the type of thrombosis; in patients with marantic thrombosis or with mild thrombophlebitis the affected limb is usually pale, with a glossy skin, and cooler than its fellow. Occasionally there is marked cyanosis, and frequently the superficial veins are dilated. In the severer infective types of thrombophlebitis the skin may be reddened, and the surface temperature of the affected limb may be considerably higher than that of the unaffected one. The œdema does not usually pit as easily as the œdema of heart and kidney disease, but is firm and elastic.

In typical cases there may be considerable variation from the above picture. The affection may be entirely latent. Almost any of the symptoms and signs may be absent. The constitutional symptoms, especially in old, feeble individuals with cachexia, may be lacking. The pain may be absent or so slight that it is entirely disregarded or attributed to some other cause. The œdema may be so slight that it is overlooked. It is usually in thrombosis of the deeper and smaller veins, such as those of the calf, that the entirely latent forms occur. Thrombosis of larger veins may be disregarded by the patient, but will usually be discovered by a careful observer. The signs may be masked, as in cardiac disease, by changes like œdema due to the original malady. On the other hand, the general symptoms, especially in the primary infective thromboses, may be intense and partake of the character of a violent sepsis.

The *course* of peripheral venous thrombosis varies considerably with the nature of the exciting cause and of the disease which preceded this complication. In cases associated with severe sepsis or with the terminal stages of debilitating diseases, death often takes place before a chance for retrograde changes is offered. In the ordinary thrombosis accompanying infectious diseases, in which recovery follows, the acute symptoms usually begin to subside by the end of the first week, the pain and tenderness become less severe after four or five days, the œdema becomes less marked, and the fever and constitutional symptoms abate. Where the local infection is severe the subsidence of active symptoms is often much slower. The lasting effects upon the limb will be considered under complications. The thromboses of the upper extremities are often less severe and recover more quickly than those of the lower extremities.

The *diagnosis* of peripheral venous thrombosis is, in characteristic cases, a simple matter. The sudden onset with localized pain, the palpable tender vessel, the evidence of disturbance in the venous circulation, and

the œdema make recognition easy. In patients with thrombosis of small, deep-seated veins, when the vessel is not palpable and there is no marked œdema, diagnosis is more difficult. The differentiation from embolism will be discussed under that head; it is only necessary to say here that in thrombosis the arterial pulsations can still be felt, and that gangrene, so common in embolism, is very rare in thrombosis.

Thrombosis of the Superior Vena Cava.[1]—The majority of instances are associated with compression of the vein by tumors, aneurism, or chronic inflammatory disease involving the vessel in cicatricial tissue. The symptoms depend on the degree of establishment of the collateral circulation and in most instances the immediate consequences of the thrombosis are so severe that death rapidly ensues. Osler states that the clinical picture in individuals who survive and establish a collateral circulation appears under one of two types. In one class of cases the patient has for years complete compensation with good health, followed by the sudden appearance of urgent symptoms, usually attacks of dyspnœa with recurrent effusion into the pleural cavities. In the second group symptoms of obstruction of the venous circulation are constantly present. In Osler's first case there was pain in the chest with swelling of the face on exertion, cough, and cyanosis. The patient died of tuberculosis. Dilatation of the superficial veins is a prominent feature in these cases. The veins concerned in the collateral circulation vary according to the situation of the thrombus. If this occurs distal to the azygos vein the collateral circulation takes place, according to Forel, mainly through this vessel. In Osler's case there was marked enlargement of the lateral thoracic veins and the superficial epigastric veins which carried the blood from the subclavian into the common iliacs.

Thrombosis of the Inferior Vena Cava.—Autochthonous thrombi are rare in the inferior vena cava and thrombosis usually results from propagation of thrombi from affluents, or from compression of the vein by neoplasm, aneurism, or the products of inflammation. Thrombosis occasionally results from compression at the point of passage through the diaphragm as the result of sagging of this muscle from the weight of a left-sided pleural exudate. Disease of the vessel wall, either simple phlebitis or new growth, may cause thrombosis of the vena cava, and occasional instances after the infectious diseases have been noted. Compression by the enlarged head of the pancreas is a rare cause.

Thrombosis of the inferior vena cava, even when complete, may fail to produce symptoms in old or prostrated individuals in the terminal stages of some debilitating disease with great enfeeblement of the circulation. Usually there is a well-marked œdema of the lower extremities, especially of the back, without ascites. The œdema may be unilateral, as has been noted by Schlesinger. This may be due to congenital duplication of the vena cava or some peculiarity in the communication between the veins of the upper and one lower extremity. It may occur because the thrombus in the vena cava is propagated from the iliac on one side, is parietal, and does not occlude the other iliac. Sometimes the œdema

[1] Osler, *Johns Hopkins Hosp. Bull.*, 1903, xiv, 169.

does not occur on one side because an old thrombus of one iliac vein has led to the formation of a collateral circulation. Involvement of the renal veins may cause a diminution in the secretion of urine, with albuminuria and hematuria, but, as Welch points out, these symptoms do not always appear. Involvement of the hepatic veins may lead to portal obstruction with enlargement of the liver, splenic tumor, and ascites. In patients who survive, an extensive collateral circulation is established. This may involve only the deeper veins, rendering diagnosis impossible, or more commonly the superficial veins of the groins and trunk take part. In cases with the superficial compensatory circulation the communication between the affluents of the inferior vena cava and the superior vena cava is carried on by the epigastric veins, the circumflex iliac veins, the long thoracic veins, the internal mammary veins, the intercostal veins, the external pudic vein, and the lumbovertebral anastomotic trunk of Braune. The deep anastomosis is carried on by the azygos and hemi-azygos and the lumbar veins.

Thrombosis of the Renal Vessels.—This will be considered with embolism, as the results are the same. Thrombosis of the renal veins is not infrequent and may be autochthonous, then usually associated with renal disease or debilitating conditions, or may be due to the extension of a thrombus from the inferior vena cava.

In many instances thrombosis of the renal vein is not followed by marked symptoms. Welch states that it is the exception for a patient to present symptoms referable to the lesion. This lack of symptoms is most likely to be present when the thrombus forms gradually, as there are abundant anastomotic channels and a collateral circulation is rapidly established. In some patients thrombosis of the renal veins is followed by symptoms so definite that a diagnosis may be made without difficulty. Briefly stated, the more important symptoms are pain in the region of the kidney, marked albuminuria, usually accompanied by hematuria and decreased amount of urine with a high specific gravity, and an enlarged, tender, palpable kidney. The pain may be very severe and may persist for weeks. Long after its disappearance the kidney may still be tender on palpation. The increase in size of the kidney may be very considerable, and it may be a simple matter to palpate it. The albuminuria is the most constant urinary change, and the amount of albumin may reach as high as fourteen pro mille by Esbach's albuminometer. In patients who recover, albumin may be present after a period of two or three months. Hematuria is not constant and is said by Hutinel to be much less liable to occur in children than in adults. It may be marked enough to be evident on examination of the urine with the naked eye. It persists a much shorter time than the albuminuria, usually disappearing in a week or two. Fever and the accompanying constitutional symptoms occur with thrombosis of the renal veins in some instances. Bilateral thrombosis of the renal veins leads to anuria followed by death.

Thrombosis of the Mesenteric Vessels.—Thrombosis of the mesenteric veins may either be secondary to portal thrombosis or may originate as a primary process in the branches of the veins. The primary form may

be due to local or to general causes. The local causes take the form of inflammatory lesions of the intestinal wall, such as ulcers, or occur as enlarged mesenteric glands or pancreatic or gastric tumors causing thrombosis from compression. Occasionally local disease of the vessel wall, either simple phlebitis or luetic inflammation, is present. Of the general causes the infections, and especially typhoid fever and the various forms of sepsis must be mentioned. Thrombosis of the mesenteric vein not infrequently follows embolism of the arteries.

The *symptoms* of thrombosis are essentially the same as those following embolism of the mesenteric arteries except that they are, if anything, more severe. In 5 out of the 157 cases collected by Jackson, Porter, and Quinby,[1] there were no symptoms referable to the abdomen. The most prominent symptoms in the average case are pain, nausea and vomiting, either diarrhœa or constipation, or both at different stages, abdominal tenderness, and signs of intestinal obstruction. Abdominal *pain* is present in the great majority of instances, and in over one-half of the patients is general in character. Localized pain when present is most common in the upper abdominal zones, either in the epigastrium or about the umbilicus. Radiation of the pain is fairly common, but there is no particular distribution which is characteristic. The onset of the symptoms is usually sudden, and there is often a constant dull ache with exacerbations of severe colic. The cause of the pain is thought to be the contraction of the intestinal wall, and its spasmodic character makes it analogous to the pain of angina pectoris or to attacks of intestinal colic from abdominal arteriosclerosis (angina abdominis). Nausea and vomiting are not necessarily present, and are more apt to be severe when the thrombosis occurs suddenly. The character of the vomitus depends on the severity and duration of the case, normal stomach contents being vomited early; later bile, fecal material, or even pure blood. Diarrhœa is present in only 50 per cent. of the patients, and in 41 per cent. blood occurs in the stools at one time or another. The diarrhœa is preceded or succeeded by obstipation in a small percentage of patients. Obstipation alone occurred in 22 per cent. of the cases collected by Jackson, Porter, and Quinby. It is at times followed by diarrhœa, usually with bloody passages. Abdominal tenderness occurs in 70 per cent. of the patients, and in a large majority is, like the pain, generalized. When localized it is most likely to occur about the umbilicus, in the cecal region, or in the epigastrium. Distension is a late symptom and is practically always generalized. Leukocytosis and iodophilia were present in the Boston cases. The temperature varies; it may fall below normal, but not infrequently fever is present. Rare signs are glycosuria and purpura.

The *diagnosis* is usually difficult, inasmuch as in but few cases the majority of the symptoms are present. In a large number of cases the diagnosis of intestinal obstruction is made. The most characteristic signs are stated to be the sudden onset of colicky abdominal pains with a fall in the temperature and passage of blood-stained stools, and later symptoms of intestinal obstruction with distension of the abdomen and

[1] *Jour. Am. Med. Assn.*, vol. xliii, No. 3.

perhaps some ascites. Thrombosis of the mesenteric veins is not infrequently associated with thrombi elsewhere in the body, and may be directly secondary to portal thrombosis. The presence of such thrombi elsewhere or of symptoms referable to thrombi should make the diagnosis more simple. Aside from intestinal obstruction, the condition may be confounded, on account of the vomiting and passage of blood, with gastric or duodenal ulcer or with disease of the heart and liver, accompanied by passive congestion in the abdominal organs. Differential diagnosis in these cases must rest upon the presence of other signs of these diseases. Patients in whom purpura is present in association with thrombosis of the mesenteric veins might be confused with instances of abdominal crisis in connection with purpuric skin eruptions of the erythema group.

Thrombosis of the Portal Vein.—This may result from disease in the vein itself or much more commonly from pathological processes which cause compression of the vessel. In the vessel wall a sclerotic process comparable to arteriosclerosis has been occasionally described, but is quite rare. Usually portal thrombi not due to external pressure are of the propagated variety, are often although not necessarily septic, and are commonly associated with intra-abdominal inflammatory processes, especially appendicitis. Thrombosis from pressure may occur in connection with neoplasms of the head of the pancreas, the stomach, the omentum, or the lymph nodes in the hilum of the liver. Another group is associated with compression by cicatricial tissue either within the liver, as in cases of cirrhosis, or external to that organ, but surrounding the portal trunk. In the latter instance the scar tissue results from a localized peritonitis which may be due to gall-stones, gastric or duodenal ulcer, or tuberculosis. Gall-stones themselves have occasionally been situated so as to compress the portal vein and lead to thrombosis. A certain number of instances of portal thrombosis without apparent cause have been recorded, the so-called idiopathic portal thrombosis, but Ponfick thinks that some of these are traumatic.

The *symptoms* of pylethrombosis are very different in septic and non-septic cases. Septic or suppurative pylephlebitis results in the formation of multiple abscesses in the liver, and the outcome is usually a rapid and fatal termination. *Appendicitis* is so frequently the exciting cause of this form of portal thrombosis that the French school speak of it as "le foie appendiculaire."[1] The clinical picture is that of sepsis with local symptoms pointing to the liver. The onset is often sudden, with a violent chill, high fever, and profuse sweating. The fever persists during the course of the disease, but is usually marked by exacerbations, often with chills, which may occur daily at about the same period, or may be more frequent and irregular. Quite early, as a rule, gastro-intestinal symptoms appear, nausea and vomiting with perhaps diarrhœa, which according to Dieulafoy may be paroxysmal. Constipation may, however, be present throughout. Jaundice and tenderness in the region of the liver are usually prominent signs, and as the disease progresses the liver may reach twice its normal size. The icterus varies in intensity, and may appear early in

[1] Dieulafoy, *Clinique Médicale de l'Hôtel Dieu*, 1897–98.

the disease or not until late. The patients finally pass into a typhoid state and die in collapse or may succumb with the symptoms of cholemia.

The form of portal thrombosis associated with simple pylephlebitis gives rise, in the majority of instances, to a clinical picture resembling that of atrophic cirrhosis of the liver. In some patients, as in the remarkable one reported by Saxer,[1] most extensive thrombosis of the main branches of the portal vein may occur without characteristic symptoms. Usually enlargement of the spleen, ascites which recurs rapidly after tapping, and the formation of a collateral circulation are prominent features. The collateral circulation may involve the superficial veins of the abdomen and lower chest, and is then plainly apparent, or it may occur through the left coronary vein of the stomach, the œsophageal veins, the intercostal veins, and the azygos veins. In the latter instance large varices may form beneath the mucous membrane of the stomach or lower end of the œsophagus, and such patients are apt to suffer from sudden and severe hematemesis or melena. The ascites which is so prominent a feature in some patients may be lacking in those in whom such hemorrhages occur. On the other hand, patients with well-marked ascites do not usually have the gastric and intestinal hemorrhages. The minor manifestations of portal obstruction, anorexia, nausea, and intestinal disturbances, may be present, especially in long-standing cases. Jaundice does not occur unless complications are present. A few patients recover as the result of the formation of a fully compensating collateral circulation, but as a rule a fatal termination is to be expected either from severe gastric or intestinal hemorrhage, from gradually increasing asthenia or from extension of the thrombosis or involvement of the mesenteric vessels and infarction of the intestine. When the process comes on gradually and gives rise to a picture of chronic portal obstruction, it may be impossible to differentiate it from atrophic cirrhosis of the liver, especially as this organ is often, although not invariably, decreased in size in cases of portal thrombosis. In the acute cases the rapid onset in an individual with a previously clean record, the absence of an alcoholic history, the absence of decrease in size of the liver, or even the enlargement of this organ, the early appearance of ascites and its rapid recurrence after tapping, or the presence of severe gastric or intestinal hemorrhages—all suggest a portal thrombosis rather than cirrhosis.

Thrombosis of the Hepatic Veins.[2]—Attention has been called in recent years, especially by Chiari and his pupils, to a form of thrombophlebitis of the hepatic veins which has not as yet been described in this country, but which is probably not very uncommon. It is overlooked no doubt because the symptoms and the gross pathology are essentially those of hepatic cirrhosis. The disease attacks both sexes alike, usually during young adult life, and seems at times to develop upon a luetic basis. Postmortem examination shows in most cases an obliterating endophlebitis of the hepatic veins usually associated with thrombosis. Not infrequently thrombi are also present in the branches of the portal

[1] *Cent. f. allgem. Path.*, 1902, xiii, Nr. 15.

[2] Hess, *Am. Jour. Med. Sc.*, 1905, cxxx; Umbreit, *Virchows Archiv*, 1906, clxxxiii.

vein. The gross and microscopic picture, aside from the changes in the veins, closely resembles that of atrophic cirrhosis.

The *symptoms* as a rule appear gradually, although in rare cases an acute onset with death in less than two weeks has been noted. Usually a sense of pain and discomfort in the hepatic region or the upper abdomen is the first thing noted. Later symptoms suggestive of atrophic cirrhosis occur, the abdomen gradually enlarges, ascites develops, and gastro-intestinal disturbances may appear. The signs of a compensatory circulation may be apparent in the form of a caput medusæ. Hematemesis and melena occur in rare instances, much less commonly than in portal thrombosis. Hematuria has been occasionally noted. Examination shows the presence of fluid in the abdominal cavity, which if withdrawn, rapidly reaccumulates. It usually has the characteristics of a simple transudate but is occasionally hemorrhagic. The liver is enlarged, smooth, and firm, in the early stages; later it becomes contracted and more or less nodular. Jaundice is generally absent. The spleen is enlarged, hard, and easily palpable. In the final stages general anasarca may appear. There is as a rule no fever, and the urine is negative. In most patients the course is shorter than that of an ordinary cirrhosis, the average duration after the onset of symptoms being about six months.

Hess states that no case of this disease has been diagnosed during life, most patients having been considered to be suffering from cirrhosis of the liver. Two acute cases with marked gastro-intestinal symptoms and prostration were diagnosed as poisoning in one instance and intestinal obstruction in the other. According to Hess, the main points in distinguishing hepatic thrombophlebitis from cirrhosis are its occurrence in younger individuals, the absence of the cause of cirrhosis, the presence of pain in the hepatic region, the rapid development of ascites, and the frquency with which paracentesis is needed.

Thrombophlebitis of the Umbilical Veins.—The occurrence of infection of the umbilical veins in the newborn child is one of the most serious diseases of early life. The condition is often insidious in onset, for, as a rule, there are no marked local signs in the umbilical stump. In occasional complicated cases pus can be squeezed from the severed end of the vein, but this is exceptional. It is stated by some observers that the more severe the infection the less the likelihood of marked local symptoms. Usually the symptom which calls attention to the condition is a gradually intensifying jaundice, which is often accompanied by symptoms of sepsis. Later hemorrhages may occur, most often from the stump of the umbilical cord. Fever may be marked. There may be inflammation of the serous membranes, pericarditis especially, and occasionally gangrene of the umbilical stump, or erysipelas of the skin surrounding it. The inflammation usually extends to the veins of the liver and causes a diffuse hepatitis or multiple abscesses of the liver. The prognosis is very grave, much more so than that of the more frequent umbilical arteritis.

Thrombosis of the Vessels of the Spleen.—Thrombosis of the main trunk of the splenic artery occurs very rarely, although this vessel is frequently the seat of arteriosclerosis. Thrombi in the smaller arterial branches give rise to the same symptoms as emboli, and will be considered under that

head. Thrombosis of the main trunk of the splenic vein is rare. Thrombi in the smaller branches of the vein occasionally cause infarcts. Septic thrombosis of the splenic vein may occur in connection with infectious processes in the pancreas from the contiguity of the vessel to that organ. The vein may be thrombosed as a result of typhoid fever. The condition is of pathological rather than clinical interest.

Thrombosis of the Pulmonary Vessels.—Thrombi in the pulmonary veins are common enough in the areas involved in inflammatory conditions of the lung, infarcts and tumors, and in emphysema. They occasionally give rise to emboli in the systemic circulation. Thrombi in the pulmonary arteries, even when they cause blocking of medium-sized branches, often, as Newton Pitt pointed out, give rise to no marked changes in the lung. When changes occur they resemble both clinically and pathologically those due to embolism, and will be considered under that head.

The occurrence of *arterial thrombosis* has been discussed to some extent under the heading of various diseases concerned in its etiology. The symptoms so closely duplicate those of embolism that the two conditions will be considered together.

Thrombo-angeitis Obliterans.—The importance of this form of thrombosis has been emphasized in recent years by the studies of Erb in Germany and of Buerger in New York. The condition is one which is characterized by the formation of parietal, red thrombi, especially in the arteries of the lower extremities, which tend to organize and to lead to the production of a collateral circulation when complete obstruction occurs. The veins, also, are involved, and in some instances recurrent attacks of thrombophlebitis simulating phlebitis migrans occur in these vessels. The process is very much more prevalent in the male than in the female sex, usually occurs after forty, is especially likely to attack Jewish people, and is possibly associated with exposure to changes in temperature and the excessive use of tobacco. Syphilis plays a doubtful part in the etiology.

There are two main clinical manifestations: (1) The condition usually described as intermittent claudication or intermittent limping, and (2) juvenile or presenile gangrene. In typical cases with *intermittent claudication*, the patient complains, on attempting to walk fast, of paresthesia and pain in the feet, tension, pain, and stiffness in the calves, coldness of the feet, and increased difficulty in walking which finally results in the severer cases in the patient stopping to rest. After a period of rest, the patient is able to proceed but any attempt at hurry results in a recurrence of the symptoms. Examination reveals diminution or absence of pulsation in the arteries of the feet, often associated with definite thickening of the vessels and with certain vasomotor phenomena in the form of pallor or, sometimes, intense redness of the affected limb. In some cases the vasomotor changes closely simulate erythromelalgia or Raynaud's disease.

The second type of case is characterized by *gangrene* of the lower extremities, occurring at an age much earlier than that at which senile gangrene appears. The gangrene may be preceded by the manifestations of intermittent claudication or it may appear spontaneously. Symptomatically

it does not differ from other forms of gangrene. It is associated with severe pain, and the affected portions present the cold blue appearance and subsequent necrosis characteristic of other forms of gangrene.

Capillary Thrombosis.—This is of pathological rather than clinical interest. The possible relationship of capillary thrombi in the kidney glomeruli to disturbances in the secretion of urine, as suggested by Welch, seems worthy of further investigation. The relation of capillary thrombi to gastric hemorrhage and to ulcer and the so-called gastric erosions has been suggested by von Eiselberg and others, but needs confirmation.

Cardiac Thrombosis.—The diagnosis of the ordinary parietal cardiac thrombi from any direct effect they may produce upon the heart itself is generally considered to be impossible. The presence of parietal cardiac thrombi may be suspected when, during failure in compensation without distinct evidences of valvular endocarditis, symptoms of embolism occur in organs supplied by the systemic circulation. Pedunculated thrombi and ball thrombi may be associated with sudden death with symptoms of syncope. In other instances ball thrombi are believed to give rise to symptoms which permit of a possible diagnosis, although it is doubtful if a correct diagnosis has been made during life. The symptoms are essentially those of an exaggerated mitral stenosis, marked dyspnœa, cough, an unusully feeble pulse, and evidences of venous engorgement out of proportion to the degree which is usual in uncomplicated mitral stenosis. Localized gangrene of the foot, which von Ziemssen described in his patients and considered almost pathognomonic, is not necessarily present. The physical signs are those of mitral stenosis, although the presystolic murmur is said to be absent in some instances, and, when present, to show a marked tendency to intermittency. As diagnostic points, von Ziemssen emphasizes the physical signs of mitral stenosis, the occurrence of the ordinary clinical signs of this lesion is an exaggerated form, especially a very small and feeble pulse, and circumscribed gangrene of the foot.

Sequelæ of Thrombosis.—Aside from those instances in which the symptoms essentially represent the sequelæ of thrombosis, as in thrombosis of the portal or hepatic veins, the remote results of thrombosis of the vessels of the internal organs are as a rule unrecognizable, for if the changes in the affected organ are not sufficient to cause death they are subsequently compensated for by the unaffected portions of the viscus, or, in cases of paired organs, by the uninvolved one. Changes in the central nervous system due to thrombosis are not, of course, followed by recovery of function if the lesion is at all extensive. Certain remote effects of peripheral thrombosis, and especially of peripheral venous thrombosis, need brief discussion. Of peripheral arterial thrombosis it need only be stated that the sequelæ are the same as of arterial embolism.

The important sequelæ of peripheral venous thrombosis may be considered under two heads: first, the occurrence of secondary embolism, and, second, the local effects. The factors which influence secondary embolism have already been briefly discussed in connection with the disease associations of thrombosis. As a general rule septic thrombi are more apt to give rise to secondary emboli than bland ones, and certain forms of thrombosis are commonly associated with embolism, while in

others this sequel is almost unheard of. Thus puerperal thrombosis and chlorotic thrombosis commonly result in secondary embolism, while syphilitic thrombosis almost never does so. Typhoid thrombosis is one of the forms in which secondary embolism is rather unusual, as it is in idiopathic recurrent thrombosis. There is, too, apparently some difference in the likelihood of embolism according to the vein affected. Haward's table shows secondary embolism most frequently after thrombosis involving the iliac veins, next in frequency after saphenous and femoral thrombosis, and only occasionally after thrombosis of the veins of the leg or of the viscera. The fact that the danger of embolism can be greatly increased by sudden movements on the part of the patient or by undue manipulation of the affected vein should be kept in mind.

Of the local complications of peripheral venous thrombosis, the perivascular suppuration has already been mentioned. Much more important are the more or less disabling sequelæ which may occur when a large vessel like the femoral is permanently plugged. In patients who have suffered from such a lesion there may be present for years, even during the remainder of life, certain annoying symptoms. The most common of these are a feeling of heaviness and clumsiness in the limb, œdema, especially at night and after exercise, stiffness of the joints, and impairment of the circulation with coldness of the member. Changes in the muscles of the limb, usually in the form of atrophy, are frequent; rarely a well-marked hypertrophy of the muscles results. To these symptoms must be added pain, which may be present along the course of the thrombosed vessel or may be more widespread, and is especially apt to invade the territory of the sciatic. Usually slight, the pain may be intense, neuralgic in character, and quite intractable. At night or after exertion distressing cramps in the muscles may be present.

Diagnosis and Prognosis.—The diagnosis and prognosis of thrombosis vary so much according to the disease associations and the vein affected that a general discussion of the subject is impracticable. The main points will be found in the discussion of the disease associations and of the symptomatology of thrombosis of different vessels.

Treatment.—This practically resolves itself into the treatment of peripheral thrombosis and of one or two forms of visceral thrombosis in which operative interference may with propriety be essayed. The *prophylaxis* of thrombosis has not as yet been seriously considered, and it is hard to see how this can be done unless we are to regard all patients suffering from certain diseases as possible candidates for this complication. We have as yet no way of telling what patients are likely to develop thrombosis, nor are we sure that the underlying factors are the same in all instances.

The immediate treatment of patients with peripheral thrombosis consists of the immobilization of the limb and in such symptomatic treatment as is demanded. The limb must be placed in a comfortable position and the immobility must be absolute, the necessity for this being strongly impressed both upon the patient and the attendants. So far as the patient is concerned, he must not only be warned against sudden movements, but also against straining at stool and excessive coughing, and if necessary, laxatives or pulmonary sedatives may be administered to aid

him. Mechanical methods must be employed to fix the limb, and at the same time pressure in the immediate neighborhood of the thrombosed vein must be avoided. This may be done by the application of a well-fitting, properly padded splint, or, after wrapping the limb in cotton wadding, by fastening it to the mattress by means of bandage strips. The use of bandage strips has the advantage over the use of the splint of allowing easy access to the limb with a minimum of manipulation. The only symptom likely to demand treatment at the onset is *pain*, which may be intense. Morphine hypodermically is the only remedy of value in severe cases but its use is seldom necessary after two or three days. This general treatment may be supplemented by the local application of an ice-bag or of hot fomentations. Belladonna ointment applied along the course of the vein or 30 per cent. ichthyol in lanolin has been recommended. The application of cold compresses moistened with normal saline solution for two or three hours daily during the second week is also recommended, as are applications of lead and opium lotion. All local medication should be applied with the greatest care.

In the treatment of peripheral thrombosis after the acute symptoms have subsided the important question to be decided upon is how long absolute immobility is to be maintained. The French school especially, who have given much thought to the matter, insist that many of the ordinary local sequelæ of thrombosis may be avoided by beginning passive motion and massage early. The three indications for beginning active treatment are, according to Quénu,[1] absence of fever for three weeks, disappearance of local tenderness over the affected vessel, and progressive decrease in the œdema. The plan outlined by this writer is as follows: During the first week that movement is permissible, only passive motion is allowed, consisting of gentle superficial rubbing and gentle movement of the different joints of the affected limb. During the second week massage of the muscles, avoiding the region of the vessel, and more marked passive motion of the joints are employed, although marked flexion of the joints in the neighborhood of the thrombus should be guarded against. During the third week the restraining bonds or splint may be gradually removed, so that at the end of this week all mechanical restraint has been removed and the patient is allowed to move the limb gently in bed. During the fourth week the patient may be allowed to increase the movements of the limb in bed, and finally to get up. The limb should at first be supported by a bandage, preferably one of some light elastic tissue, as the heavy stockings used on patients with varicose veins may hinder the formation of the collateral circulation. The use of some support, preferably a cane, will be necessary when the patient begins to walk, but may be discarded as power and confidence are regained.

In patients in whom œdema and pain persist for a long time after convalescence, these symptoms may require special treatment. For the œdema the use of massage and electricity and the wearing of a light supporting bandage are necessary. For the pain the application of tincture of iodine over the painful points, local warm douches or warm

[1] *La Semaine medicale*, July 26, 1905.

baths, and the use of electricity are of value. The latter remedy may be applied in the form of the high-frequency current, or if pain is not very marked the constant current in doses of from 25 to 50 ma. may be passed through the limb for some fifteen or twenty minutes daily. Faradization applied so as to produce intermittent contractions of the muscles over a period of ten to fifteen minutes daily may be of use in some patients in whom the pain is slight. According to Cleaves, electrical treatment should be begun during the latter part of the acute stage of thrombosis. The continuous current is first used in doses not to exceed 5 ma. for a few minutes daily. The current must have an unvarying rate of change, and must be capable of producing long, wave-like, undulatory, muscular contractions. In chronic cases when a whole leg or arm is stiff and œdematous, the indifferent contact is best made at first by placing the foot or hand in a 1 per cent. saline bath at 100° F. charged from the indifferent pole. The active contact is made by a hand electrode which is passed over the affected limb. After a week or two the indifferent contact may be placed over the lumbar enlargement so as to apply the stimulant directly through the nerve supply. Treatment should be applied at first daily for ten minutes in doses of 8 ma., gradually increased as the treatment progresses to 20 ma. The treatments may be reduced in number after the first two weeks, first to two or three a week and later to weekly treatments. Usually from one and a half to three months' treatment is necessary. The sinusoidal current may be used as an adjunct during the later stages of the treatment. Internal medication is of no value except in special forms such as luetic thrombophlebitis.

The surgical treatment of peripheral thrombosis has been suggested by Moullin in patients in whom the superficial veins are involved, and by Briggs in idiopathic recurrent thrombophlebitis. Moullin[1] has been in the habit of excising the whole thrombosed vessel in such cases, and claims that it shortens the period of illness and removes the risks of secondary embolism, deep thrombosis from extension, and recurrence in the same vessel. There seems no reason why his method should not be more extensively employed in selected cases.

Treatment of thrombosis of *visceral vessels* must in most instances be purely symptomatic. The chances of detachment of emboli from thrombi in visceral veins is slight; nevertheless, absolute rest in bed should be required when visceral thrombosis is suspected. In the case of mesenteric and portal thrombosis, there is hope that operation will save a small percentage of patients. The mortality after operation is at present 92 per cent. (Jackson, Porter, and Quinby). Without operation, however, the patient is almost certainly doomed, and with increased skill in diagnosis and improvement in technique the percentage of successes can doubtless be increased. The operation chosen should be one which can be quickly performed with a minimum chance of shock. The procedure recommended by Jackson, Porter, and Quinby, *i. e.*, bringing the involved intestine into the wound, resecting with liberal margins, and fixing the open edges in the wound, seems most logical. It is possible that the Talma

[1] *Brit. Med. Jour.*, 1904, ii, 1688.

operation or permanent peritoneal drainage might be of value in thrombosis of the portal or hepatic veins provided a diagnosis could be made early enough.

Treatment of Thrombo-angeitis.—The treatment of thrombo-angeitis obliterans requires separate consideration. In order to prevent the progress of the disease it is necessary to warn the patient to avoid tobacco, the exposure of the affected limbs to heat or cold, and the avoidance of damp weather and severe exercise. The dietetics of this disease are the same as those for arteriosclerosis. Local applications in the form of galvanic foot baths, hot carbonated baths, and light massage are of value. Small doses of iodides have been recommended and cardiac tonics may be necessary in patients with feeble circulation. In patients with gangrene, amputation is usually necessary and care should be taken to amputate well above the line of gangrene. By the use of Moskowicz's test the point of election can be determined. The test consists in putting on an Esmarch bandage high up on the effected limb and then removing it. On its removal the blood immediately flows into the well-vascularized portion of the limb which is separated by a line of demarcation from the poorly-vascularized portion. This line of demarcation is the point of election for the amputation.

EMBOLISM.

The term embolism is applied to the obstruction of an artery, vein, or lymphatic from the lodgement in its lumen of undissolved foreign matter carried there by the circulation. The mass producing the obstruction is spoken of as an embolus.

Etiology.—This resolves itself into a consideration of the sources and incidentally the varieties of emboli. It may be well first to consider briefly in a general way the phenomena of embolism. Usually emboli are composed of detached particles of thrombi, and the seat of their lodgement depends on their point of origin. They may be arrested in the systemic arteries, in the pulmonary artery, or in the portal vein. Generally emboli which lodge in the systemic arteries originate in the left side of the heart, in the main arterial trunks, or rarely in the branches of the pulmonary veins. Under some circumstances it is believed that minute systemic emboli may originate in the venous system, passing through the large pulmonary capillaries. Emboli which lodge in the pulmonary artery usually originate either in the systemic veins or in the right side of the heart. Occasionally they originate from non-occluding parietal thrombi of the main branches of the pulmonary artery itself. Emboli which lodge in the portal vein originate in the affluents of that vessel. Ordinarily emboli lodge only in arteries, or in vessels like the portal vein which have peculiarities of distribution like an artery. Ordinarily, too, emboli in the systemic circulation originate only on the left side of the heart, in the larger arteries, or in the pulmonary veins. There are two exceptions to these general rules which must be briefly considered.

Venous emboli have been noted occasionally, usually in veins without valves, and are most common in the subclavian vein, the innominate

vein, the axillary vein, the pulmonary veins, the venæ cavæ, the hepatic veins, the cardiac coronary veins, the cerebral sinuses, the mesenteric veins, and the veins of the pampiniform plexus. They are spoken of as "retrograde" emboli, as they are due to the transportation of a thrombus formed elsewhere in the venous system in a direction opposite to the usual course of the blood stream. The cause of these retrograde emboli is probably a backward flow of the venous current due to the sudden temporary stoppage of the return flow of the blood to the heart.

The second exception is the so-called "*paradoxical*" embolus, also spoken of as the "*crossed*" embolus. This name is applied to an embolus lodging in an artery of the systemic circulation which originated in the systemic veins or the right side of the heart and passed through an open foramen ovale. This form is very unusual.

Origin of Emboli.—All emboli are not composed of detached particles of thrombi, for various substances may gain entrance to the circulation and obstruct the bloodvessels. These may be divided into two great groups according to their origin: *endogenous* emboli, which originate within the heart or bloodvessels, and *exogenous* emboli, which have their origin outside of the circulation. Both groups may again be subdivided, according to their nature, into bland or inert emboli, and active emboli, the former being harmless aside from their purely mechanical action, the latter being either infective or composed of living cells or of parasites.

The bland endogenous emboli are usually broken-off particles of bland thrombi, but may consist of detached fragments of calcareous material, of particles of detritus from atheromatous abscesses or ulcers, of pieces of clot from aneurisms or from the heart valves, or of material originating from the destruction of blood corpuscles or of blood parasites such as the malarial plasmodium.

The bland exogenous emboli may be of a solid, liquid, or gaseous nature. Solid emboli originating outside of the vascular system are very rare. There is one remarkable case on record in which a revolver bullet entered the circulation and acted as an embolus. Of the liquid emboli, the most common are fat emboli, usually seen after fractures, but also observed after concussion of the body, inflammation of the subcutaneous fatty tissue, and sometimes after infections. Certain semiliquid or liquid substances introduced subcutaneously for medicinal or cosmetic purposes, such as oil, bismuth salve, mercurial preparations, and paraffin, may also give rise to emboli. Gaseous emboli may be due to the introduction of atmospheric air into the veins during operations or after labor, but in many instances so-called air emboli are due, as Welch has shown, to the production of gases within the circulation by gas-forming bacteria.

The active emboli, like the bland ones, may originate either within or without the circulation. In the first group may be mentioned emboli of leukocytes and emboli originating from infective thrombi. In the second group emboli composed of body cells of various kinds, notably of cells from the bone-marrow, placenta, or liver, are not infrequent, and are sometimes spoken of as autositic emboli. Parasitic emboli are, of course, frequent in bacterial infections, especially in anthrax, glanders,

tuberculosis, leprosy, and malignant œdema. The higher forms of vegetable parasites, as the moulds and actinomyces, may also form emboli. Finally, animal parasites, as the larvæ or ova of filariæ, trichinæ, strongyloides, flukes, and teniæ, may obtain entrance to the circulation and produce embolism.

Pathology.—Site of Deposit of Emboli.—It is not to be assumed that all particles free in the circulation succeed in lodging in a vessel. Rarely such particles become entangled in the meshwork formed by the chordæ tendineæ or the columnæ carneæ. Still more rarely large emboli may lodge in the auriculoventricular orifices. It is also to be borne in mind that the caliber of the embolus is often much greater than that of the vessel it obstructs, either because a long, thin embolus becomes folded, thus increasing its diameter, or because an embolus by lodging crosswise on the partition at the point of division of the vessel (riding embolus) interferes with the circulation of two branches at once.

Emboli free in the blood stream do not lodge indiscriminately in any vessel, but the vessels of certain organs seem especially prone to be plugged. The data are subject to error, for they relate to emboli which have caused distinct lesions, whereas many emboli produce no appreciable gross lesions. Welch believes that the systemic arteries going to the lower extremities receive more emboli than vessels elsewhere. There is a tendency for infective emboli to occur in those places where the circulation is naturally slowest, as in the liver, and also to create lesions in some *locus minoris resistentiæ*. Various lists have been prepared giving the sites of predilection of bland emboli but these frequently do not agree. According to Welch, the vessels most commonly affected are, in the order of frequency, the pulmonary, renal, splenic, cerebral, iliac, and arteries of the lower extremities, axillary and arteries of the upper extremities, cœliac axis and its hepatic and gastric branches, central artery of the retina, superior mesenteric, inferior mesenteric, abdominal aorta, and coronary of the heart. The vessels most frequently affected are either those in direct line of fire from the commonest origin of emboli, venous thrombi, or those supplying organs whose cells are most easily injured by disturbances in their blood supply. The action of gravity, the weight and size of the embolic mass, and the degree of obliquity with which branches are given off from the main arterial trunk, are the most important of these mechanical factors influencing the lodgement of emboli. Changes in the walls of the arteries, such as roughening from atheroma or narrowing from external pressure, also doubtless play a part in many instances.

Anatomical Characters.—The appearance of emboli varies with their character and age. When seen soon after their lodgement, they are generally easily distinguished from thrombi, but if they have been long in the vessel, so that a secondary thrombus has formed about them, the distinction may be impossible. The fresh embolus is distinguished from the thrombus by its more or less irregular shape, by its lack of adhesiveness or slight adhesiveness to the vessel wall, and by the fact that it may have the appearance of tissue from an old thrombus and that at some point on its surface there is often evidence that it has been

detached from a larger mass. The secondary thrombus which usually forms about an embolus causes it to become adherent to the vessel wall, and it then on casual observation appears like an ordinary thrombus. Incision into such a plug may show that the central portion has a much older appearance than the periphery, and may even be calcified, but convincing evidence on this point is often lacking. The most important point in doubtful cases is the detection of a source for an embolus, and unless care is taken this can easily be overlooked. It is impossible in some instances to detect the primary thrombosis, but it is often missed because certain veins which are commonly the seat of thrombi, such as the pelvic veins, are not carefully examined in the ordinary autopsy. The condition of the vessel and the clinical history must also be taken into account in reaching a conclusion.

Effect on the Tissues of the Lodgement of an Embolus.—In certain vessels supplying vital organs, such as the main branches of the pulmonary arteries or of the coronary arteries of the heart, the lodgement of an embolus is usually followed by sudden death. Aside from such special vessels, the changes produced by the lodgement of an embolus depend upon the character of the cells and the circulation of the affected tissue, and upon the character of the embolus. Bland emboli produce merely mechanical effects; active emboli produce in addition chemical and sometimes vital changes.

The effect of the lodgement of bland emboli in the vessels of certain organs and tissues with an extensive and freely anastomosing blood supply, and cells which bear well temporary interference with their nourishment, may be quite inappreciable. Thus emboli of the vessels of the liver, the thyroid, the bones, the urinary bladder, the female genital organs, and the more vascular portions of the skin, result as a rule, in a temporary anemia quickly followed by the formation of a collateral circulation.

Bland emboli in tissues whose circulation is anatomically terminal, or is insufficient to supply blood by collaterals to cells easily succumbing to the effects of anemia, result in necrosis. The type of necrosis produced varies according to the character of the structure affected, and its relations to the surrounding tissue. If the part whose circulation is cut off is segregated from the rest of the tissues, as occurs after embolism of the main artery of an extremity, the resulting process is known as gangrene or mortification. If the affected tissue is a small segment of an organ, and is surrounded by normal tissue from which lymph can flow into it, the result will be either an area of softening, as occurs in the central nervous system, or, if large quantities of coagulable material are absorbed by the necrotic cells, coagulation necrosis in the form known as an infarct. In certain structures, as the kidney, spleen, brain, intestine, and retina, infarction almost invariably takes place. In others, perhaps on account of individual peculiarities in the circulation, it does not always occur. Thus bland emboli in the lungs do not usually produce infarcts. Bland emboli of the larger cerebral arteries, on account of the circle of Willis, often produce but little effect. Embolism of the main vessels of the extremities, and even of the aorta itself, may not result in necrosis.

When infarctions occur their appearance is not always the same owing to individual peculiarities in the cells or tissues of certain organs. In general, *infarcts* have a conical shape with the base of the cone toward the periphery of the organ, this being due to the fact that they correspond to the distribution of the branches of the particular arterial trunk which has been plugged. Their consistency varies somewhat with the character of the organ, being not quite so firm in a loose-meshed organ with chances for expansion as in a compact one enclosed in an unyielding capsule. The main variation, however, lies in the color, which may be red (hemorrhagic) or white (anemic). Some describe mixed infarcts, and in the kidney, where the distribution of the vessels in the medulla is different from that in the cortex, a white infarct with a red apex may occur if the infarcted area is partly included in the medullary zone. The factor which makes the difference between the red and the white infarct is the presence in the infarcted area of red blood corpuscles, and the character of the cells of the affected organ, or sometimes other peculiarities of structure, determine whether red blood cells shall be present in numbers. In the kidney soon after the blood supply is shut off from the affected part, the sensitive cells die and absorb serum from the small amount of blood carried in by the scant collaterals. As a result the cells swell rapidly, compress the cortical vessels, and prevent any marked influx of blood. We therefore usually get white infarcts in the kidney. Very much the same thing occurs in the brain, whose cells are even more sensitive to interference with their blood supply than those of the kidney. Here instead of a white infarct we get an area of white softening. In the spleen, on the other hand, the interference with the blood supply irritates the muscle fibres in the capsule and trabeculæ, and causes them to contract, forcing out the blood. After a certain period, perhaps some days, the muscle relaxes, but by this time changes in the walls of the vessels have occurred. They are no longer able to retain the blood, which escapes into the affected area and swamps it with serum and corpuscles, resulting in stasis and finally necrosis. In the lung the element of infection comes into play, the bacterial toxins producing changes in the vessel walls which allow the passage of the blood into the alveoli. Here also stasis and necrosis result. Microscopically the tissue in infarcted areas has the usual appearance of necrotic tissue, except that usually the structure of the affected organ is at first to be made out perfectly. As the infarct grows older, signs of reaction on the part of the surrounding tissue, the wandering in of leukocytes, and proliferation of the connective-tissue cells, become apparent.

In a good many instances infarction occurs only during the terminal stages, but sometimes patients survive for a long period after it has occurred. In such patients infarctions undergo a process of organization similar to that already described under Thrombosis, and the infarct is replaced by a cone-shaped patch of scar tissue very much smaller than the original infarct. Such scars are common enough in the kidneys, are less common in the spleen, and are rare in the lungs, as pulmonary infarcts are almost always forerunners of death. Certain bland emboli, such as air, fat, and parenchyma cell emboli, produce special effects.

The effect of the lodgement of the so-called active emboli depends on their nature. The most important of them are the infective emboli, emboli of tumor cells, and parasitic emboli.

Infective emboli produce the same mechanical effects as bland emboli, and in addition changes due to the action of the contained bacteria and their toxins. As in other infections two factors are to be considered; the virulence of the infective agent, and the resistance of the individual. Inasmuch as the virulence of the bacteria in infective emboli may be slight, and the resistance of the individual to infection may be great, we find that many infected emboli produce only mechanical effects. Not only the general resistance, but also variations in the local resistance are to be reckoned with. Such variations differ to some extent in individuals of the same species, and to a more marked extent in individuals of different species. Where the individual resistance is lowered or the bacteria in the emboli possess a high-grade of virulence, we see, besides the ordinary mechanical effects, the production of hemorrhages, of extensive necrosis, of metastatic abscesses in the tissues in which the emboli lodge, and, if putrefactive bacteria are present, of areas of gangrene.

Embolic Aneurisms.—One of the rarer complications of embolism is the production of embolic or mycotic aneurisms. Such aneurisms usually occur as a result of the direct action of pyogenic bacteria contained in infected emboli on the walls of the affected artery. This causes a partial destruction of the coats of the vessel and a consequent weakening. Rarely the traumatic action of sharp emboli of calcific material may lead to aneurism formation, but this form is very unusual. These aneurisms may develop upon any vessel, but are naturally more prone to occur in those vessels which are lacking in support from surrounding tissue. They are more common for this reason in such arteries as the mesenteric, the more superficial peripheral arteries, and the cerebral arteries. The aneurisms are usually associated with general sepsis, especially sepsis with endocarditis.

Of the other varieties of active emboli, those of tumor cells and of animal parasites deserve brief mention. *Tumor cells* may gain entrance to the circulation either by direct growth into the bloodvessels or indirectly by way of the lymphatics and the right heart. In some types of tumor, notably certain neoplasms of the testicle and kidney, it is not unusual for extensive growths to penetrate the veins, from which they may extend even to the cavities of the heart. Large masses may be detached from such tumor thrombi and may cause fatal embolism of the pulmonary arteries. Ordinarily, however, tumor emboli are small, so small that they are more apt to lodge in the capillaries than elsewhere. Those originating in the general circulation usually gain entrance to the veins and naturally tend to be arrested in the lungs, although probably a fair percentage of them pass the large pulmonary capillaries and get into the general arterial circulation. Paradoxical emboli of tumor cells are not very uncommon. In the case of tumors of the abdomen arising in organs whose vessels drain into the portal system the liver is naturally the seat of the most extensive deposits of neoplastic emboli. A good many tumor-cell emboli die, but in many instances they cause

metastases. Aside from the lungs and liver, the bones, the kidneys, and the skin seem especially liable to be the seat of such secondary embolic nodules.

Certain *animal parasites* or their ova may act as emboli. Of the smaller ones, the malarial parasite is the most common. In the pernicious type of malaria, the capillaries of the brain are often plugged with parasites. Occasionally they accumulate in the kidney vessels, as shown by Ewing, and the writer saw one case in which the smaller pulmonary vessels appeared as if injected with them. The *Amœba dysenteriæ* has also been observed in the bloodvessels, and some amœbic abscesses of the liver probably originate from emboli of amœbæ in the branches of the portal vessels. Emboli of the larger parasites or their ova are more common in the lower animals than in man, although the *Trichina spiralis* during certain stages of development occupies the vessels, as evidenced by the œdema which accompanies trichinosis. Echinococci occasionally act as emboli, and in the lungs are stated to produce special symptoms.[1]

Symptoms.—The symptoms produced by the lodgement of an embolus, vary according to the character of the obstruction and the function and structure of the tissue involved. Certain symptoms of a local and general character common to all varieties of emboli may be briefly considered here. *Pain* is an almost constant accompaniment of embolism of the peripheral vessels, but is less common in embolism of visceral vessels. In many instances it is very abrupt in onset, and the patient may experience the sensation of a sudden painful blow. In some cases it is not very marked, but it may be intense. It is doubtless due at the onset to the mechanical action of the embolus on the nerves of the affected vessel from impact and stretching, but later in infective emboli the direct action of the bacteria or toxins on the vessel wall plays a part. In both bland and infective emboli the anemia of the area supplied by the embolized vessel also accounts for some of the pain, as it causes irritation of the sensory nerves. Pain of a secondary character, due to the production of inflammation in the involved tissues, occurs in connection with septic emboli. Evidences of interference with the circulation are not visible except in emboli of the vessels supplying the extremities or surface of the body. They may appear indirectly, however, in pulmonary embolism in the form of hemoptysis, in mesenteric embolism as hemorrhagic diarrhœa, and in embolism of the renal artery as hematuria. Evidences of impairment of function in visceral embolism are often slight or absent, except in the case of organs such as the central nervous system, in which definite functions are associated with sharply localized areas. Embolism of the vessels of other internal viscera may be accompanied by impaired function if large areas are thrown out of action. If only a small area is affected the lesion is compensated for by the uninvolved portions of the organ, or in the case of paired organs, by the normal one. General symptoms such as chills, fever, headache, and rapid heart's action, are not usually marked except in connection with septic emboli,

[1] Garnier and Jomier, *Presse méd.*, 1905, i, 369.

and are due to the sepsis. Slight fever and acceleration of the pulse may occur as a result of bland emboli.

Air Embolism.—The association of sudden death with the entrance of atmospheric air into the veins has long been known. As a rule it only occurs when veins of a fair size and situated near the heart are opened. It is therefore especially liable to occur in connection with operations on the neck, not only because the veins of the neck are near the heart, but also on account of the fact that these vessels are held open by their relation to the fascia, and because the aspiration of the thorax acts forcibly here and tends to suck in relatively large quantities of air in a short time. Air embolism has also been described in connection with wounds of other superficial veins, usually of the upper extremities or the head, and as a complication of operations on the uterus during the puerperium, or even of simple intra-uterine douching. Rarely air embolism has been reported as a complication of gastric ulcer.

A large number of supposed cases of air embolism will not stand critical inspection. Welch and Flexner[1] pointed this out in an article on the *Bacillus aërogenes capsulatus*, remarking "that of the considerable number of reported cases of suspected entrance of air into the bloodvessels, none seem to have been previously the subject of bacteriological study." Cases of supposed air embolism after labor or in connection with diseases of the gastro-intestinal tract must be scrutinized with special care, for in both these situations infection with the gas bacillus has been shown to be not infrequent.

Making due allowance for infection with gas-forming bacteria, there remains a certain number of cases in which no doubt exists that the entrance of air into the veins caused death. Experimental work on the lower animals has shown that it is possible to cause death in this way, although in dogs, the animals usually employed, large amounts of air are required, and the chances of producing a fatal result are greater the nearer the heart the air is introduced. The cause of death, according to Wolf,[2] is nearly always pulmonary embolism, although occasionally coronary or cerebral emboli cause the fatal result. As a rule the air does not penetrate beyond the pulmonary capillaries, and Wolf seems inclined to throw out of the category of air embolism cases in which air was found in any quantity in the general circulation.

The *symptoms* of air embolism in well-marked cases are striking and easily recognizable. Usually during the course of an operation on the neck the surgeon is suddenly startled by the sound produced by the entrance of air into a severed vein. This is described by Koenig as a "lapping" murmur. In some instances the patient dies with lightning-like rapidity; in others death is preceded by signs of apprehension, dyspnœa, cyanosis, trembling, dilatation of the pupils, syncope, and convulsions. A distinct churning sound, which Wolf believes is due to the mixture of air and blood being pressed behind the columnæ carneæ or being forced through the pulmonary valves, may be heard in many cases on auscultating over the heart. The symptoms last but a few

[1] *Jour. Exp. Med.*, 1896, No. 1.
[2] *Virchows Archiv*, 1903, clxxiv.

seconds, and most patients die, although recoveries are recorded. The cases of E. Janeway and Hun, in which cerebral symptoms followed the introduction of peroxide of hydrogen into the thoracic and abdominal cavities respectively, should possibly be classed with air embolism.

Fat Embolism.[1]—Most commonly met with after fractures of the long bones, emboli of fat have also been encountered after orthopedic operations, especially brisement forcé, after ordinary surgical operations and operations on the bones, after contusion or laceration of the subcutaneous fatty tissue, and in association with infections with fatty degeneration of the organs, with atheroma of the arteries, and with diabetes mellitus. The complication has also followed the subcutaneous introduction of oil for purposes of nutrition. The view generally held regarding the origin of fat emboli associated with fractures has been that they originate as a direct result of the entrance of fat into the vessels at the point of local injury to the bone. Ribbert[2] claims that the amount of fat found in the lungs is too great to have originated in this way, and he explains the lesion as due to the escape of fat from the general jarring of the bones. The fat emboli are found in some patients merely in the lungs; in others, after an interval of one or more days, some of the emboli pass on and lodge, especially in the muscle of the right side of the heart and in the brain. In these situations they produce areas of hemorrhage and fatty degeneration probably sufficient to account for the cardiac and cerebral symptoms. The emboli also lodge in the spleen and kidneys. Here they do not produce any appreciable symptoms, though fat is commonly excreted with the urine in the case of kidney involvement.

Symptoms of fat embolism are in most instances lacking, although in severe cases sudden death may ensue. In a certain number of patients symptoms definite enough to allow of a diagnosis occur. These may appear immediately after the injury, but are usually delayed from six hours to fifteen days. Where immediate symptoms appear they are pulmonary and take the form of a rapidly fatal asphyxia. Commonly the patient, who has perhaps reacted from the shock of the fracture or operation, is noticed to be breathing more rapidly than normal, appears anxious, may be restless, or on the other hand somnolent, and may complain of pain in the side. Sometimes hemoptysis is present. Examination shows the appearances often ascribed to shock; pallor, perhaps cyanosis, a cold skin and a rather feeble, rapid, and irregular pulse, and probably slight elevation of the temperature. In severe cases contracted pupils, diminished reflexes, Cheyne-Stokes respiration, convulsions, and coma may occur, and death may close the scene. Localized signs of consolidation of the lung with a few rales may be present. They are most apt to be heard posteriorly over the bases of the lungs. The presence of fat in the urine is an important diagnostic sign, and fat may be found in the sputum also. In a patient seen with my colleague, Dr. Sanford, there was a slight leukocytosis, 14 per cent. of the cells being neutrophilic myelocytes.

[1] Connell, *Jour. Am. Med. Assn.*, February 25, 1905.
[2] *Deutsch. med. Woch.*, June 28, 1900.

The *prognosis* is uncertain. The mortality from fat embolism after fractures is probably not over 1.5 per cent. The diagnosis is not necessarily difficult. It may be confused with shock or with ordinary embolism, but shock occurs much sooner after the operation or injury than does fat embolism, and ordinary emboli are a late complication. The presence of fat in the urine is of diagnostic value, but may occur without symptoms of fat embolism. If associated with localized lung signs, slight fever, rapid pulse, and respiration, and mental unrest or somnolence, these symptoms appearing from six to seventy-two hours after a fracture, the probabilities are in favor of fat embolism. In operative cases the differentiation from the effects of anesthetics may be difficult, and sepsis may be suspected in patients with a good deal of fever.

Cell Emboli.—Apart from emboli of tumor cells, there have been described for the last twenty years or more emboli composed of the cells of normal organs or tissues, and more recently emboli of phagocytic cells associated with infectious diseases. Of the normal cells, those of the liver, placenta, and the bone-marrow are the ones most commonly found as emboli.

After injuries, not only cells but actual fragments of liver tissue and bone-marrow may be transported, and even whole chorionic villi have gained access to the circulation. In typhoid fever large phagocytic cells may gain entrance to the portal circulation, as the studies of Mallory[1] show, and MacCallum[2] has demonstrated that the same cells may enter the lungs through the thoracic duct. Most cell emboli lodge in the pulmonary vessels, but a few reach the general circulation through an open foramen ovale. These emboli are not usually large enough to cause lesions of an extent sufficient to produce clinical symptoms, though occasionally they may cause quite extensive pulmonary infarction.

Mercurial Emboli.—The introduction of the use of insoluble mercurial salts by the hypodermic route was soon followed by evidence that embolism at times resulted. The accident occurs after the use of the salicylate of mercury, of gray oil, of calomel, and of other insoluble preparations, especially when paraffin is used as a vehicle. The frequency of the complication is hard to judge but it probably occurs in about 1 per cent. of patients so treated.

The *symptoms* depend upon the point of lodgement in the lungs, the emboli which lodge peripherally causing involvement of the pleura and therefore pain. In such cases the characteristic symptoms are the sudden onset, soon after the injection, of paroxysmal cough, with lancinating pain in the side, sometimes chilly sensations, and usually fever. In some instances no symptoms appear for at least twenty-four hours after the injection. Fever may be absent, and, if the emboli are deep-seated, pain is not usually present. The physical signs of a patch of consolidation associated with rales may sometimes be detected. The *diagnosis* is obviously simple, although it must be borne in mind that in cases of fresh luetic infection fever, chilly sensations, and anorexia may follow the injection of mercury without the presence of lung emboli. The

[1] *Jour. Exp. Med.*, 1898, iii, No. 6.
[2] *American Medicine*, March 21, 1903.

prognosis is so uniformly good that some syphilographers take it for granted that the complication will occur and consider it no obstacle to the hypodermic use of mercury. According to Heidensfeld, embolism may be avoided by using lanolin as a vehicle for the mercury. Similar emboli may follow the use of bismuth paste in sinuses.

Paraffin Emboli.—The subcutaneous use of paraffin for cosmetic purposes has been followed in several instances by paraffin embolism of the central artery of the retina. The complication usually ensues immediately after the injection of the paraffin. The patient may show marked symptoms of collapse and sudden loss of sight on one side. The loss of vision is usually permanent. According to Stein[1] the complication may be avoided by using only soft paraffin, injecting it only when it has a pasty consistency, and never using more than 3 cc. at a sitting.

Embolism of Special Arteries.—Embolism of the Pulmonary Artery.—This is the most frequent form of embolism and is much more common than thrombosis of this vessel. Pulmonary emboli occur most frequently in connection with heart disease, usually originating from thrombi in the right side of the heart, and in connection with certain forms of peripheral venous thrombosis, especially the puerperal type and some other varieties mentioned in the article on thrombosis. Occasionally pulmonary embolism arises from the detachment of portions of parietal thrombi in the larger branches of the vessel itself. The symptoms produced by the lodgement of an embolus in a branch of the pulmonary artery depend mainly upon the size of the vessel which is obstructed. Blocking of the trunk or of one of the main branches usually results in sudden death. This may occur at once, but is often delayed a few seconds, during which time the patient is almost apnœic, is gasping for breath, deadly pale, and practically pulseless. The sufferer may cry out at the time of lodgement of the embolus, and may grasp the precordial region with an expression of great anguish. In a few rare instances occlusion of the main trunk has occurred without causing immediate death or marked changes in the lungs.

When a medium-sized branch is plugged, or when an embolus lodges in a large branch, but does not completely occlude the lumen of the vessel, the patient may survive for hours or days, or may even recover completely. The most prominent symptoms in these patients are the rapid respiration and the marked dyspnœa, both of which in the early stages are out of all proportion to the signs of pulmonary involvement. The dyspnœa and the intense sensation of oppression in the chest which accompanies it, recall cardiac dyspnœa, but the rapidity of onset of the symptoms in embolism and their great intensity are points of distinction. Lancinating pain in the chest may be present in patients with embolism of this type, but it is unusual. It may be absent at first, but present later in patients who survive long enough for the development of pleural involvement. The physical signs vary in such patients at different periods. At first the patient is pale, later often markedly cyanotic, extremely restless and anxious looking. A marked effect on

[1] *Deutsch. med. Woch.*, 1903, vol. xxxix, Nrs. 36–37.

the circulation is apparent from the first. The heart is weak, perhaps irregular, and the pulse is small, feeble, and very compressible. Systolic and diastolic murmurs at the base of the heart have occasionally been described. Physical signs in the lungs are at first absent. After twenty-four hours, if the patient survives that long, there may be impaired resonance over a part or the whole of one lobe, usually a lower lobe. This is generally accompanied by feeble breath sounds and a few fine, moist rales which later may become much more numerous. At the time the definite lung signs develop the patient may have a profuse, frothy, or bloody expectoration, but this usually disappears in a few days. There is often some fever, although this is not as a rule high. The mind is usually clear, although convulsions and coma may precede death in fatal cases. Recovery may occur in patients with severe symptoms. Leopold reports the case of a patient who recovered after three severe attacks.

Obstruction of the smaller branches of the pulmonary artery when associated with chronic passive congestion or pleural effusion, leads in many instances to the formation of a hemorrhagic infarct. Such infarcts occur in nearly 50 per cent. of all cases on the right side at the base of the lung.

Symptoms of pulmonary infarction are not always present. In some instances the lesion is entirely latent. In other cases the symptoms which accompany the embolism of a large pulmonary vessel are present in a modified form. There is a sudden attack of pain in the side, usually the right, with a rigor or chilly sensations, an increase in dyspnœa, rise in the temperature, and perhaps bloody, or, at any rate, blood-streaked expectoration. True hemoptysis in the sense of the expectoration of pure blood is rare, but blood-streaked sputum is not uncommon, and should always suggest infarction in a patient with heart disease in the stage of broken compensation. Physical signs can be detected in a great many patients with pulmonary infarction, as the lesion is most common at the bases of the lungs, which are accessible to exploration, and because most infarcts involve the periphery of the organ so that there is no zone of normal lung tissue over the lesion. The detection of certain signs, such as definite dulness or changes in the fremitus, depends on the size and situation of the infarct. On palpation, as a rule, marked signs are absent, although in case of a large infarct superficially situated, the fremitus is generally decreased. One or more circumscribed areas of dulness may often be made out. The dull note not infrequently has a tympanitic quality, this being due at times to the collapsed condition of the lung about the infarct and at times to the transmission of resonance from a large bronchus through the consolidated lung. Auscultation during the early stages may reveal fine crepitant rales, although these do not usually last long. The breath sounds over the area of consolidation may be feeble or almost lacking or, if the area is in contact with a fair-sized bronchus, there may be marked bronchial breathing. As a result of atelectasis of areas about the infarct, crackling rales may be heard. A pleural rub may be heard when the infarct is superficial.

The *diagnosis* of pulmonary embolism involving the larger vessels is based on the sudden onset of intense pulmonary symptoms in a patient

suffering from some disease which is commonly associated with venous or cardiac thrombosis. The more prominent of these diseases and the frequency of their association with embolism has been noted in the article on Thrombosis. In women the puerperal state and chlorosis should always be regarded with suspicion, and in both sexes patients should be watched during and after the infectious and cachectic diseases, local diseases of the veins, cardiac disease, and abdominal operations. The source of the emboli in many cases is obscure.

The *prognosis* in pulmonary embolism is always grave. In the puerperal form 60 per cent. of the patients die, according to Richter. Embolism in chlorosis has a prognosis even graver than this. Recovery from embolism of the larger branches of the pulmonary artery is very rare, although it does occur. Recovery after smaller emboli with infarction is also uncommon. According to Romberg, of 43 patients with heart disease and signs of lung infarction observed in his clinic, 36 died. The prognosis depends not only upon the size and character of the embolus, but also upon the general condition of the patient.

Embolism of the Splenic Artery; Splenic Infarction. — The appearance of an infarct in the spleen is often unaccompanied by characteristic symptoms or signs. In some instances the diagnosis can be made. The most important signs are sudden pain in the splenic region, with enlargement of the spleen. Sometimes the onset is accompanied by a definite rigor. Vomiting is not uncommon, according to Leube. Pain is not always present. The swelling of the spleen is not usually very marked, but the organ is generally palpable, and there may be a localized point of special tenderness with an overlying friction rub due to localized peritonitis. Fever is not marked unless the infarct is a septic one, in which case there may be a high fever a few days after the onset of signs, and chills may occur. When suppuration follows a septic embolus, marked signs of local peritonitis may occur and there may be general peritonitis from rupture of the purulent focus. Even with bland emboli there are sometimes very marked signs of local peritonitis. The presence of a source for embolism will, of course, have great weight in the diagnosis.

Renal Infarction.—This is often latent but in some instances definite evidences of kidney involvement are present. The most important of these are changes in the urine and pain and tenderness in the kidney region. In bilateral infarction of the kidney there may be complete suppression of urine, but this never occurs in unilateral infarction. As a rule there is some diminution in the quantity of urine, with the presence of large amounts of albumin and perhaps some blood. Schmidt states that hematuria is quite uncommon. It is perhaps overlooked in some instances. The absence of casts or marked sediment may be a striking feature of albuminuria from embolism, and is probably due to the fact that no urine is secreted in the infarcted area and nothing is therefore washed out of it. The occurrence of pain, sometimes intense, is not infrequent in connection with kidney infarcts. At times it is described as burning or as a sensation of pressure. Its very sudden onset is often suggestive. It is situated as a rule in the kidney region, radiates but little, and is never referred to the external genitals or to the

shoulder-blades. It is more constant than the pain of ureteral calculi. The pain is associated with marked tenderness in the kidney region and may be increased by coughing, deep breathing, and vomiting.

The *symptoms* of kidney infarct may be confounded with those of Dietl's crisis from movable kidney, with pain accompanying the sudden congestion of a tumor of the kidney, or with the pain of an acute exacerbation of a chronic nephritis. The pain in the infarct is usually more severe than that accompanying an exacerbation of an old nephritis, and is more marked on pressure. The onset of a Dietl's crisis often follows exercise, while the pain of infarct often appears while the patient is in bed. Other conditions, such as gall-stone colic, lead colic, and ureteral colic might cause confusion but the differential points readily suggest themselves. Evidence of some source for an embolus is very important in making a diagnosis.

Embolism of the Mesenteric Arteries.—Embolism of the mesenteric arteries has been considered under the head of Thrombosis.

Embolism and Thrombosis of the Aorta.—Embolism and thrombosis of the thoracic aorta are of extremely rare occurrence, for with the great force of the blood stream through this part of the circulation it is only very exceptionally that a thrombus can form or an embolus gain lodgement. Complete obstruction of the thoracic aorta is followed by death, usually very suddenly, at latest after a few hours. Incomplete obstruction either produces no appreciable symptoms, or, if marked, leads to the same changes which characterize obstruction of the abdominal aorta together with, in some instances, signs of blocking of the arteries of the upper extremity.

Embolism and thrombosis of the abdominal aorta are best considered together, for although there exist instances in which the gradual progress of the disease seemed to show that thrombosis was the lesion, it is often impossible to determine whether the obstruction is due to a thrombus or an embolus. Thrombosis of the aorta may suddenly give rise to very acute symptoms and embolism may rarely occur without signs of sudden onset. The thrombi occupy as a rule that portion of the abdominal aorta which lies below the point of origin of the main branches, *i. e.*, below the origin of the mesenteric arteries. This part of the vessel is considerably narrower than the rest of the main trunk and is the section in which, under conditions of enfeebled circulation, the best chances for the formation of a thrombus or the lodgement of an embolus are to be found. Most cases of aortic thrombosis are associated with disease of the vessel wall, usually arteriosclerosis, while of the cases which appear to be embolic—and these constitute a large majority—the greatest number are associated with mitral stenosis. When this latter lesion is present there is frequently evidence that thrombosis has been present somewhere in the left side of the heart, and while this is sometimes lacking, aortic emboli originate in most instances in this situation. In other cases external pressure plays a part, or the embolus is furnished by a thrombosed aneurism of the thoracic aorta.

The *symptoms* of obstruction of the aorta vary. In some patients with aortic thrombosis the symptoms are obscure and cannot be definitely

referred to a lesion of the aorta. In patients with definite symptoms, these may be gradual or sudden in onset. When the onset is gradual it is believed by some observers that the patient may survive two, three, or even four years after the appearance of the first symptoms. Mazoux lays stress on the importance of intermittent claudication as an early sign of the gradually progressing form of thrombosis of the abdominal aorta.[1] As the disease progresses this symptom becomes more and more marked and may be associated with severe pain in the lumbar region radiating to the limbs. There may be sensations of numbness and formication in the feet. Finally a paraplegia of the lower extremities develops, usually followed by gangrene of parts of one or both lower limbs. The character of the paraplegia is not well described in many of the reports. Usually it seems to be incomplete, limited movements of the limbs being possible. The state of the reflexes varies; in some patients they are abolished; in others, the paralysis being spastic, they are presumably increased. The occurrence of gangrene is preceded first by coldness and pallor, later by cyanosis of the extremities, and in some cases by chronic ulcerations. Usually severe pain in the legs is an accompaniment of the gangrene. The extent of the mortification varies in different patients, this probably depending in part on the completeness of the obstruction of the aorta, in part on the number and distribution of collateral vessels. Œdema is not marked, as a rule, and may be absent.

In patients in whom the onset of aortic obstruction is acute—and these constitute the majority—*pain* is usually the most prominent of the early symptoms. It is generally intense and referred to the lower extremities. The patient may be struck as by a shock and fall to the ground in intense anguish. In most instances there is a markedly anxious expression. Occasionally pain is absent, and, on the other hand, it sometimes occurs in paroxysms separated from one another by periods of several days. Other symptoms are very variable. Usually there is pallor of the skin of the extremities, followed by lividity, diminution of sensation, paresis and finally paralysis of the muscles, and gangrene. The pulsation in the vessels of the legs is very feeble or entirely absent. General symptoms may occur. The intense pain may cause marked psychic disturbances. There is sometimes a gradual rise in the temperature. The pulse usually becomes distinctly weaker and more rapid than it was before the onset of the symptoms. If the renal vessels are involved symptoms of renal infarction or even total suppression of urine may occur. Involvement of the mesenteric arteries will produce the intestinal symptoms already described under Mesenteric Thrombosis. Pain in the lower abdomen and tenderness over the aorta are not infrequently present.

In the *diagnosis* of a typical case there is hardly any doubt. Some of the more chronic cases might, at some stages, suggest Raynaud's disease, but the fact that only the lower extremities are affected, the progressive character of the lesion, and the lack of arterial pulsation should rule this out. In patients without much pain an acute myelitis might be sug-

[1] Mazoux, *Thrombosé de l'Aorte, Thèse de Paris*, 1905.

gested, but the pallor of the skin, the cold lower extremities, and the absence of pulsation in the vessels of the legs should prevent this mistake.

The *prognosis* is exceedingly grave. Very few patients have recovered. Death may take place the same day that the symptoms appear; usually the end comes within fifteen days from the onset. Some patients, however, live several weeks, and a few survive several years after the symptoms first manifest themselves.

Embolism and Thrombosis of the Subclavian Artery.—Embolism of the large branches of the arch of the aorta is extremely rare, most instances of obstruction being due to thrombosis.

The *symptoms* of obstruction of the subclavian artery are very variable, and, considering the size and importance of the vessel, the lack of striking symptoms is often the most marked feature. There may be paroxysmal neuralgic pain in the neck and shoulder on the affected side, and this may be markedly influenced by changes in the weather. Occasionally there is distinct weakness of the arm which may almost amount to paralysis. The objective signs are the result of the obstruction to the circulation. The pulsation in the radial artery on the thrombosed side is in some instances not influenced in the least; in other patients the *pulsus differens* may occur. The pulsation in the carotid artery on the affected side is usually unimpaired, although it may be a little weaker than normal. In some patients changes in the skin are present in the form of great dryness, or sometimes a patchy œdema. There may be a wasting of the muscles of the arm. Gangrene is usually absent, and its presence is stated to indicate that the process is a luetic one.

The *diagnosis* can only be positively made during life by palpation of the arteries on each side with the demonstration of lack of pulsation in one of them. In a few instances a thrombus may extend into the axillary or brachial arteries and the vessels may be felt as firm cords.

Embolism and Thrombosis of the Carotid Artery.—Embolism of the common carotid artery is very unusual, the internal carotid being much more frequently affected. Thrombosis is more common than embolism, and is usually associated with arteriosclerotic changes in the vessel wall. Occlusion of the carotid is of interest on account of its relation to the cerebral blood supply. As has been abundantly proved by ligature of the vessel during operations on the neck, the effect of obstruction on the cerebral circulation is usually slight, not infrequently entirely negative. The anastomoses with neighboring vessels are extensive, the most important in the case of the external carotid being the branches from the carotid of the other side; in the case of the internal carotid, the vertebral arteries and the circle of Willis. In some instances the collaterals seem to be poorly developed or unable to accommodate themselves to the increased demands, and symptoms of cerebral anemia and softening occur. The patient may complain of giddiness, and there may be convulsions, stupor, coma, and eventually hemiplegia on the side opposite the lesion. In some patients there is paralysis of one side of the face only or of one limb. Aphasia may follow thrombosis of the left carotid artery. The diagnosis may sometimes be made during life by detecting the thrombosed vessel as a sensitive cord. The rapidity with which occlusion

occurs has a bearing on the development of symptoms, and embolism is, for this reason, more apt to produce serious symptoms than thrombosis.

Embolism and Thrombosis of the Arteries of the Extremities.—A distinction between embolism and thrombosis of the arteries of the extremities is sometimes possible from the fact that in arterial thrombosis the onset of the symptoms is often gradual. It has been shown, however, that the onset of symptoms in thrombosis is frequently just as abrupt.

The *subjective symptoms* of obstruction of the peripheral arteries are quite similar to those of venous obstruction. They depend largely on the number of anastomosing vessels and the rapidity with which a collateral circulation is established. The result of plugging of peripheral arteries is less marked in the upper extremities where the collaterals are numerous, but depends also on the condition of the circulation in general and upon the presence or absence of vascular disease. Naturally the obstruction of an artery will produce quite different effects in a young, relatively vigorous individual with sound arteries and in an old, feeble person with diseased vessels. Pain is a symptom which is practically always present, is usually sudden in onset, and is often extremely severe. It is due to the stretching of the vessel, and in embolism also to the impact of the embolus. As a rule it is associated with hyperesthesia or complete anesthesia in the part rendered anemic, and disturbances of motion ranging from paresis to complete paralysis. The affected limb is usually at first pale and cold, and although œdema is often present, it is generally slight and not to be compared in degree to the œdema of venous thrombosis. Palpation of the affected artery below the point of embolism demonstrates a lack of pulsation. Tenderness of the vessel is also usually present. As time goes on, if the collateral circulation is not established, the pallor of the limb changes to cyanosis or a mottled appearance, and finally gangrene occurs. If the embolus is infective we see, besides these changes due to mechanical obstruction, perivascular suppuration, and perhaps the formation of an embolic aneurism.

The differentiation of arterial thrombosis from arterial embolism is often impossible and not of any particular importance. The differentiation of embolism from venous thrombosis is usually easy. Pain is common to both, but in embolism lack of marked œdema, the loss of arterial pulsation, the more marked sensory symptoms and paralysis, and above all the gangrene, usually leave little room for error. Besides this, a source for the embolus can frequently but not invariably be made out.

So far as the loss of a limb is concerned, the *prognosis* depends upon the artery affected and the general condition of the patient. Plugging of the arteries of the upper extremity is less serious than obstruction of the vessels of the legs. Thrombosis or embolism of the femoral or popliteal arteries almost invariably results in gangrene, whereas even the subclavian may be obstructed without gangrene of the hand or arm. Gangrene is much more apt to occur in patients with an enfeebled circulation and preëxisting arterial disease. If a patient is already enfeebled and shows evidences of embolism elsewhere, the obstruction of a peripheral artery may be the direct cause of a fatal termination. Naturally the arterial obstruction resulting from chronic heart disease with failing

compensation is much more serious than that following the infectious diseases.

Obstruction of the Hepatic Vessels; Hepatic Infarction.—The types of thrombosis of the hepatic vessels associated with clinical symptoms have been discussed. Brief mention must be made of the infarcts of the liver which, however, are not known to be associated with distinct clinical features and are of pathological significance only. Two forms of liver infarction are to be recognized; the white infarct, usually due to obstruction of a branch of the hepatic vein, but occasionally resulting from portal obstruction or rupture of the liver, and the so-called "atrophic red infarct" of Zahn, which occurs in certain cases of thrombosis or embolism of the branches of the portal vein.

Embolism and Thrombosis of the Coronary Arteries of the Heart.—Thrombosis of the coronary vessels is much more common than embolism. In view of the situation of the origins of the coronary arteries, their size, and the frequency with which degenerative changes attack their walls, it would seem that the chances in favor of thrombosis are much greater than those in favor of embolism. A few observers, Romberg for example, state that the large and medium-sized coronary vessels are most frequently obstructed by emboli, but the mass of pathological evidence contradicts this. When thrombosis does occur, it is usually associated with arteriosclerosis, and considering the frequency with which this occurs, it is strange that thrombosis is not more common. Embolism of the coronaries is usually associated with general sepsis and endocarditis, and the emboli are therefore usually infective. Bland emboli in the coronaries have been described in a few instances.

Whether the stoppage of the coronary artery is due to a thrombus or an embolus, the result is much the same, and depends partly on the size and distribution of the occluded branch, partly perhaps on the presence or absence of preceding disease of the vessel and partly on individual peculiarities in the circulation. Stoppage of the main branch of the coronary artery results in most instances in sudden death, though this is not invariably the result. There may, in fact, be obstruction of the two main branches, without any marked cardiac symptoms during life. Such instances are due to individual peculiarities in the circulation, and in most patients a fatal issue may be expected from a few seconds to a few hours after the obstruction has occurred.

When obstruction of the coronary artery is not immediately fatal it leads to changes in the heart muscle. There may be merely fatty degeneration of the area of muscle supplied by the occluded vessel, but usually an infarction results. The occasional exceptions only go to prove the rule that the coronary vessels are terminal vessels, at any rate after they have penetrated the musculature. The common site of the larger infarcts is the anterior surface of the apical one-third of the left ventricle and the septum near the apex, and this because the descending branch of the coronary artery is the one most frequently involved. Occasionally infarcts occupy the wall of the ventricle near its base, and still more rarely the right ventricle is involved. Cardiac infarcts are often irregular in shape, and generally have a characteristic yellowish color and a peculiar

dry consistency. They are often hemorrhagic about the edges. On their ventricular surface they are usually covered by a mural thrombus, while their pericardial surface is generally the site of a pericardial exudate which may later organize, obliterating the pericardial cavity over the affected area and doubtless affording some protection against rupture and aneurism formation. If the obstruction and resulting infarction are not soon followed by the death of the patient, there may be either a fatal rupture of the heart through the weakened necrotic area, or an organization of the infarct with its replacement by a patch of scar tissue. This may be able to withstand the intracardiac pressure or it may gradually give way with the resulting formation of a cardiac aneurism.

The *symptoms* of obstruction of the coronary vessels are not very characteristic, and it is only rarely that the lesion can be diagnosed during life. The sudden death which often accompanies obstruction of the larger branches is not pathognomonic of thrombosis or embolism, and may, in fact, occur in connection with coronary arteriosclerosis without actual obstruction. On the other hand, the lodgement of an embolus with the formation of a distinct infarction may be clinically latent, especially in individuals with great feebleness of the circulation. There are differences in the way in which death occurs in patients with coronary obstruction. In some the end is so sudden and unexpected that, as Krehl puts it, there is not even a change in the facial expression. In other patients the lodgement of a coronary embolus or the formation of a coronary thrombus is accompanied by symptoms of angina pectoris or of severe cardiac dyspnœa. There may be the sudden onset of a severe attack of precordial pain, with sensations of oppression, great dyspnœa, and a feeling of anxiety. Usually in these patients there is rapidity and weakness of the heart's action, with marked irregularity. In many instances such an attack is followed by death within twenty-four to forty-eight hours, sometimes with symptoms of rupture of the heart. In case the patient survives, the most prominent feature is likely to be a prolonged and gradually increasing cardiac weakness.

The *diagnosis* of coronary artery thrombosis or embolism is at best a question of probabilities. The condition should be suspected when, in an individual who has shown signs of cardiac weakness without marked dyspnœa or pain, a sudden anginal or dyspnœic attack occurs followed by death or by gradually increasing cardiac asthenia. The diagnosis being so uncertain, it is impractical to discuss the prognosis.

Embolism and Thrombosis of the Retinal Vessels.—Embolism of the central artery of the retina is no longer believed to be so common as was once taught. Many ophthalmologists now hold the opinion that the changes commonly ascribed to embolism are often due to arteriosclerosis or to spasm. The lesion is nearly always unilateral, affects the left eye most frequently, is more common in men than in women, and occurs most often in connection with cardiac disease. The changes occurring in the retina are essentially those which result in an anemic infarct elsewhere. The changes produced by the plugging of the central artery of the retina lead to a characteristic ophthalmoscopic picture. There is a marked ischemia of the retina with œdema. The pulsation of the arteries

is absent, and these vessels appear collapsed and thread-like. The veins as well as the arteries are at first narrowed, but later may be irregularly dilated. There is commonly a blood-red spot in the fovea. The disturbance in the blood supply to the optic nerve leads to atrophy.

The most characteristic *symptom* of obstruction of the central artery of the retina is sudden loss of sight. If the obstruction is complete, the blindness is also complete. In partial obstruction there may be temporary loss of vision followed later by complete loss. If a branch of the vessel is occluded, the loss of sight affects only that portion of the retina supplied by the branch. Inasmuch as the embolism ultimately results in optic-nerve atrophy, blindness is usually permanent. In some patients, either through the establishment of a collateral circulation or as a result of a breaking up and dislodgement of the embolus, a partial return of vision occurs. Thrombosis of the central vein of the retina produces very similar symptoms, although the loss of sight is at first not so marked. In this case the ophthalmoscope shows great dilatation of the veins, contraction of the arteries, papillitis with marked hemorrhages, and ultimately optic atrophy. The diagnosis and prognosis of embolism differs according to the location and character of the obstruction, and is discussed under the various forms and situations of embolism.

Treatment.—Inasmuch as by far the commonest sources of embolism are venous thrombosis and cardiac disease, preventive measures are to a limited degree possible. The latency of certain types of venous thrombosis is to be borne in mind, and in diseases like chlorosis in which obscure pains in the legs may indicate deep thrombosis, careful examination should be made, and if any suspicion of involvement of the calf veins exists the patient should be kept completely at rest. In puerperal women also, and in patients who have had abdominal operations, the possibility of thrombosis and its frequent latency should be kept in mind, and complete rest, care in avoiding straining at stool, and the avoidance of sudden movements should be enjoined until the time of danger is past. In outspoken peripheral thrombosis avoidance of manipulation of the thrombosed vein by the physician, absolute rest, the avoidance of straining and coughing, and of too abrupt movements have already been mentioned, and are more fully discussed under the treatment of thrombosis.

Little can be done to prevent the occurrence of embolism in cases of cardiac thrombosis of the ordinary parietal type. The cardiac stimulation necessary in such patients may actually increase the danger of embolism and instances in which the administration of digitalis has been followed by evidence of the lodgement of emboli are by no means unknown. In acute vegetative endocarditis, measures having a sedative effect on the heart, such as the application of an ice-bag to the precordium, render the likelihood of embolism less.

The prevention and treatment of *air embolism* require separate discussion. Inasmuch as the danger is greatest during operations on the neck, the surgeon should take special pains when operating in this situation to avoid wounding the large veins. It has been proposed by Lafargue to operate under water in such cases, but this seems impracticable. It is important to keep the wound moist, for, according to Tillmanns, air

embolism only takes place when the wound is dry. If air embolism has actually occurred, the surgeon, if observant, can prevent the entrance of further air by quickly placing the finger over the opening in the vessel, and if but a small amount of air has entered, this may suffice to save the patient from serious symptoms. If the patient shows marked evidences of air embolism, three methods of procedure are available: the direct aspiration of the air from the heart, forcing the air onward and getting it beyond the heart cavities and pulmonary vessels, and forcing the air in a direction opposite to the circulation out of the wound through which it entered. Direct aspiration of the right side of the heart has, so far as we know, been used only in animals. Its use in human beings is worth considering. Attempts to force the air onward may be made by introducing saline solution into the circulation through the wound in the vein, or may be brought about indirectly by attempting to make the patient cough or vomit. In some instances it has been possible to force the air out of the opening in the vein by rhythmical compression of the thorax, allowing the opening to remain open while the compression is being made and closing it at other times. As air embolism is so rapidly fatal, promptitude on the part of the surgeon is one of the chief considerations.

In the prevention and treatment of *fat embolism* little can be done. Inasmuch as the commonest cause is fracture of long bones, care should be taken in the treatment of such injuries to use as little manipulation as possible. In operations on the long bones also the surgeon should avoid unnecessary trauma, and in the application of brisement forcé, especially when large joints are involved, the danger from fat embolism should be borne in mind, and the procedure carried out as expeditiously as possible. The opening up of closed wounds and the ligation of vessels leading from the wound have been suggested in the treatment of fat embolism, but these procedures are little likely to lead to good results, and their application is like locking the stable-door after the horse is stolen. Attempts to emulsify the fat by the introduction of sodium bicarbonate into the circulation seem farcical considering the weak solutions which can safely be used and the tremendous dilution which must result from mixture with the blood. Efforts to dissolve the fat by the introduction of ether into the circulation must be regarded as positively dangerous considering the fact that thrombosis may be produced experimentally by the introduction of ether in this manner. After all, the most that can be done is to treat the patient expectantly, paying special attention to cardiac stimulation. There would seem to be some danger, however, in too active cardiac stimulation, for the sudden forcing of large numbers of fat emboli through the pulmonary capillaries into the general circulation might produce serious cardiac and cerebral disturbance.

The treatment of *pulmonary embolism* has for its objects first, the support of the heart, which is usually very much depressed, and, secondly, the prevention of the dislodgement of other emboli. Immediately after the lodgement of pulmonary embolus active cardiac stimulation must be employed, as at this time the cardiac weakness is often extreme and may be the cause of death. The usual diffusible cardiac stimulants must be promptly employed in adequate doses. Ammonia, ether, adrenalin,

and camphor may be given for their immediate effects, to be followed later by digitalis, caffeine, or strophanthus. The object of this cardiac stimulation is to tide over the dangerous period of heart depression. When this has been done cardiac stimulants must be used with great caution, as overstimulation may lead to the loosening of other emboli and cause a fatal issue. It is well to rely upon the milder cardiac tonics after the first cardiac depression has been overcome.

The main indication for the prevention of other emboli is absolute physical and mental rest. For this purpose morphine is generally needed at first, but after a few days the marked restlessness which often accompanies the lodgement of a pulmonary embolus usually disappears, and the milder sedatives, such as the bromides, are sufficient. The prevention of coughing by pulmonary sedatives and the prevention of straining at stool by keeping the bowels loose cannot be too strongly insisted upon. The rest for the first eight or ten days should be as nearly absolute as possible. After this limited movements are allowable, but the patient should remain in bed from four to six weeks, and avoid any violent exercise for months after convalescence is established. The diet should at first be liquid, as this allows the patient to be fed with a minimum of exertion on his part. After a week or ten days a soft diet may be allowed and this may be gradually modified until the patient is on ordinary diet. Tea, coffee, and stimulants are best avoided. Pain resulting from pleurisy, and the various complications of pulmonary embolism, such as empyema and pneumothorax, are to be treated in the usual way.

The treatment of *embolism of the arteries of the extremities* has for its object the relief of immediate symptoms like pain, and the encouragement of the formation of collateral circulation. For the pain, which is frequently very severe, morphine is generally needed, and in embolism it is often necessary to continue its use for some time, for, unlike thrombosis, in which condition the pain rapidly recedes, embolism is often accompanied by an increase in suffering with the advent of gangrene. Local applications over the vessels in the form of unguentum hydrargyri, or 30 per cent. ichthyol in glycerin or lanolin, and applications of moist heat have been recommended. In applying any local medication, direct pressure on the vessel should be avoided. Little can be done to encourage the formation of a collateral circulation unless the necessary anastomoses are present. The limb should be placed in a position which favors the flow of blood to it, moist heat should be applied to the surface, and judicious cardiac stimulation should be employed. When gangrene occurs surgical treatment is necessary. The occurrence of venous hyperemia is to be avoided. Strict asepsis should be carried out to prevent infection of the necrotic part, and finally amputation is indicated. This should not be performed until a well-marked line of demarcation has formed and the inflammation in the neighboring tissue has subsided.

The treatment of *embolism of the central artery of the retina* is unsatisfactory. It is claimed that good results have in some instances followed massage of the eyeball, the object of this being to break up the large embolus and force it from the trunk of the retinal artery into the smaller branches, where it could do less damage. The occurrence of an embolism

of the retinal artery should call attention to the danger of a similar lesion elsewhere, and demands a careful examination of the patient with the injunction, if it seems necessary, of complete rest for some time.

PHLEBITIS.

Inflammation of the veins is the most common form of vascular inflammation. The process may be acute, subacute, or chronic; may originate in the tissues about a vein as a periphlebitis, may begin as a lesion of the intima, an endophlebitis, or rarely, may start in the middle or external coats of the vessel.

Etiology.—Phlebitis is usually a secondary rather than a primary disease, and commonly results from trauma, from the direct extension of inflammation from a local inflammatory process, or from the metastasis of infectious or toxic material from foci of inflammation elsewhere in the body. Instances of so-called "idiopathic" phlebitis are not lacking, but the term "idiopathic" indicates little but a lack of exact knowledge.

The etiology of phlebitis from trauma needs no special comment. Phlebitis resulting from direct extension is common, and occurs in connection with most local inflammations. Certain forms of phlebitis from extension are especially prominent on account of their frequency and their danger. Among these may be mentioned septic phlebitis of the uterine and peri-uterine veins accompanying puerperal infection, phlebitis of the prostatic veins in gonorrhœa, phlebitis of the veins of the intestine in appendicitis, dysentery, and hemorrhoids, phlebitis of the cerebral sinuses in mastoiditis, and phlebitis of the umbilical vein in the newborn. In local inflammations of the peripheral soft parts, of bones, and of other viscera than those mentioned, phlebitis also occurs, but is of less moment because less apt to give rise to severe secondary manifestations. The exciting cause of the phlebitis is naturally the same organism or organisms which caused the original inflammation. In puerperal sepsis the streptococcus is most common, in gonorrhœa the gonococcus; in appendicitis and mastoid disease the pyogenic cocci, often associated in the former instance with the colon bacillus.

Multiple phlebitis of a metastatic character may accompany general sepsis, but the disease is most frequently seen in single vessels as a complication or a sequel of the various acute infectious or toxic diseases or of certain cachectic states. Inasmuch as in most instances this form of phlebitis is accompanied by thrombosis of the affected vessel and the symptoms of thrombosis usually dominate the clinical picture, the discussion of the etiology of thrombosis contains most of the information bearing on the cause of thrombophlebitis.

In the instances of phlebitis following anemic and cachectic conditions and associated with gout, doubt as to the exciting cause prevails. In anemia and cachexia the increased predisposition to infection produced by the primary disease is well recognized, but while there is some evidence that infection plays a part in producing the secondary phlebitis, it is not yet conclusive. In the case of gout there is, besides the general predisposition to infection, the peculiar vulnerability of the cardio-

vascular system which is so common in the subjects of this disease. Here again it is not clear whether the phlebitis is due to the same poison which causes the joint lesions or whether it is due to a secondary action of bacteria or their toxins.

Chronic phlebitis is usually associated with chronic inflammatory lesions in the neighborhood of the affected vein or with a condition of passive congestion. It may also be caused by the entrance of animal parasites or their ova into the vessels, the commonest and most characteristic example of this being the chronic endophlebitis caused by the bilharzia worm (*Schistosomum hematobium*).

In all forms of phlebitis personal predisposition must not be forgotten. There is just as much reason to believe that certain individuals have particularly vulnerable veins as that other individuals have especially vulnerable pulmonary tissue. Instances of a family tendency to vascular disease, and especially to certain forms of phlebitis, are not rare.

Pathology.—The pathological picture presented by a vein which is the seat of phlebitis varies with the duration and character of the lesion. In acute phlebitis resulting from the extension of surrounding inflammation the vessel wall is usually somewhat thickened, perhaps translucent-looking and red or grayish-red in color. Actual purulent infiltration of the vessel wall may be appreciable to the naked eye. On opening the vessel the lumen is found to be filled with a thrombus of the white or mixed variety which may be in a condition of purulent softening, or, if the process has lasted some time, may show signs of organization. The microscope shows in such a vein an infiltration of the vessel wall with polynuclear leukocytes, a spreading apart of groups of cells by the inflammatory exudate, an extensive destruction of the finer fibres of elastic tissue, and sometimes actual necrosis of patches of the vessel wall. In ordinary thrombophlebitis the process is similar, but the evidences of inflammation are less marked. The changes which occur when recovery takes place have been described in the article on Thrombosis. Regeneration of the tissues follows the organization or absorption of the thrombus and is participated in not only by muscle and connective tissue, but also by the elastica. In some instances acute phlebitis is not accompanied by thrombosis, and this is especially apt to be the case in certain types of phlebitis of the superficial veins.

In chronic phlebitis there is a thickening and stiffening of the vessel wall which may or may not be accompanied by thrombosis. This is often associated with distinct dilatation of the vessel. Microscopic examination of such a vein shows an increase in the cells of the intima which may be either diffuse or patchy, an hypertrophy of the musculature, and an increase in the connective tissue throughout all coats, but especially marked in the adventitia. There may be a marked increase in the elastic fibres of the vessel wall and the vasa vasorum may be considerably dilated and show proliferative changes in their lining endothelium.

In infection with the *bilharzia* the phlebitis which results is a pure endophlebitis. The intimal cells proliferate and produce bud-like projections which invade, and sometimes completely fill the lumen of the affected vessels. There is also proliferation of the subendothelial coat

of connective tissue. This form of phlebitis is, however, never accompanied by thrombosis.

Besides these varieties there is a special type of phlebitis which has been described by Neisser[1] and by Schwartz[2] as *phlebitis migrans*. In this type the lesion appears to the naked eye as a fusiform swelling of the wall of the vein, sharply localized, not seriously impairing the lumen of the vessel, and not accompanied by thrombosis. Under the microscope this swelling is found to be due to the infiltration of a localized area of the outer and middle coats of the vessel, with a richly vascularized granulation tissue. In Neisser's specimens, taken from patients who had a luetic history, the collections of cells were more or less closely grouped about the small vessels, and were interspersed between areas of relatively normal tissue. In Schwartz's specimens, from patients with tuberculosis and phlebitis migrans, the cell infiltration was much more diffuse.

The occurrence of specific tuberculous and syphilitic phlebitis needs only brief mention. Tuberculous phlebitis is of little direct clinical import, though its relation to acute miliary tuberculosis of the lungs renders it of great pathological significance. Syphilitic phlebitis occurs as gumma formation in the walls of the veins. It also is of pathological rather than clinical significance. There are instances on record of an obliterative phlebitis in connection with intestinal and pancreatic syphilis which is probably syphilitic in nature, but which presents no pathognomonic histological changes. It is probable that the specific nature of doubtful venous lesions may be cleared up by finding in them the *Treponema pallidum*. An extensive discussion of syphilitic phlebitis may be found in the monograph of Proksch.[3]

The favorite sites of phlebitis differ according to the cause. Traumatic phlebitis, the form following the infectious and cachectic diseases, and so-called gouty and rheumatic phlebitis usually attack the veins of the extremities, the lower extremities much more frequently than the upper, and the left side much more frequently than the right. The veins of the lower extremities are probably most frequently attacked on account of the greater chances of obstruction to the return flow of blood in them, especially in patients with feeble circulation, the greater strain to which the vessels are subjected from the action of gravity, and their greater liability to trauma. Phlebosclerosis, which is held by some authorities to predispose to attacks of acute phlebitis, is also more common in the veins of the lower extremities. The reason why the lesion occurs more frequently on the left side is not clear. Phlebitis from extension naturally occurs most frequently in those situations where acute inflammation is common, as the skin, the alimentary tract, and the lungs.

Symptoms.—Acute phlebitis may cause both general and local symptoms. The general symptoms may precede the local ones. The patient may feel unwell, and there may be a slight fever and a gradually increasing pulse rate before any appreciable local evidences of phlebitis appear. When the phlebitis is septic in origin the fever may be intense and the

[1] *Deutsch. med. Woch.*, 1903, xxix, Nr. 37.
[2] *Virchows Archiv*, 1905, clxxxii, Heft 2.
[3] *Ueber Venensyphilis*, Bonn, 1898, Handstein.

illness may begin with a chill. Ordinary cases of phlebitis do not, as a rule, have fever higher than 101.5° to 102° F., and this usually subsides a few days after the onset. Very often the occurrence of pain, most marked at the site of inflammation, but usually radiating more or less, is the first symptom. The symptoms and signs which develop after the first few hours depend upon the presence or absence of thrombosis. In most instances the vessel becomes plugged by a thrombus and the symptoms described in the article on Thrombosis occur. Thrombosis does not always occur, however, and is more commonly absent in phlebitis of superficial veins than in phlebitis of deep veins. In case it is not present the inflamed portion of the vein is apparent as a semi-elastic, tender cord, the skin over which is often reddened. There is usually some local inflammatory œdema of the tissues over the vessel. The absence of thrombosis may be tested by compressing the vein at a point between the inflamed area and the heart, and determining whether the blood is dammed back by this procedure. Phlebitis of the veins of the limb is usually accompanied by a certain amount of stiffness and disability, especially if the inflamed vein be in the neighborhood of a joint. This stiffness is due to the pain which is produced by movement of the affected limb, and is not a paresis or paralysis. When thrombosis does not occur, the acute signs of phlebitis usually begin to disappear in two or three days, and by the end of ten days or two weeks the vein may have returned to normal.

The clinical picture presented by the so-called "phlebitis migrans" is a little different from that of the ordinary acute phlebitis. Phlebitis migrans may occur during the tertiary stages of syphilis or in patients who have no specific history. It attacks by preference the veins of the upper extremities, especially those about the bend of the elbow, and appears in the form of multiple spindle-shaped swellings averaging 3 or 4 cm. in length by 1 cm. in diameter. These swellings appear along the course of a single vessel or may be distributed on several vessels. They are usually somewhat sensitive to the touch, are firm but elastic, and may or may not be accompanied by evidences of inflammation of the overlying tissue. Sometimes the skin over them is pale and free from all signs of inflammatory change; in other instances it is distinctly reddened. A slight but distinct inflammatory œdema, usually pretty well confined to the region of the inflamed patch, is sometimes present. This form of phlebitis is never associated with thrombosis. The veins distal from the the enlargement show no engorgement and there is no general œdema of the area supplied by the inflamed vessel. In a few instances sensory changes in the fingers, in the form of slight paresthesia, have been described. The peculiarity of this form of phlebitis which gives it its name is the fact that the fusiform swellings on the vessels may actually progress from one part of the vessel to another. Measurements taken from day to day have shown that the swelling may occasionally change place to a slight extent. So far phlebitis migrans has only been observed in connection with syphilis and pulmonary tuberculosis, but it will probably be shown that it is not invariably associated with these diseases.

Acute suppurative phlebitis is always accompanied by thrombosis, and besides causing the ordinary signs of thrombophlebitis, it is commonly

associated with indications of a general sepsis. There may be fever of an intermittent type, chills, profuse sweats, rapid action of the heart, and the presence of a marked leukocytosis. This form of phlebitis is most common in the deeper peripheral veins, in the hemorrhoidal veins, the uterine veins, the cerebral sinuses, and the portal vein and its branches. The symptoms of the varieties of suppurative phlebitis of medical interest are considered in the article on Thrombosis.

Chronic phlebitis gives rise to the same symptoms as the acute variety, although their intensity is less. It is very apt to be marked by a series of exacerbations, during which the pain and symptoms of inflammation become more marked, alternating with a series of remissions. It may or may not be accompanied by thrombosis, and, just as in the acute form, the symptoms will depend to a considerable extent on this factor.

Sequelæ.—These depend in the main on the presence or absence of an accompanying thrombosis. If thrombosis is absent, a complete return to normal of the vessel is frequently observed. If thrombosis is present, the element of importance is the character of the thrombus. If a bland one, it may be absorbed and the vein return to normal, or it may become organized and the local sequelæ of thrombosis may be left behind. If the thrombus is septic or associated with certain diseases, as chlorosis or puerperal infection, there is considerable danger of embolism, and this is the most serious complication of phlebitis.

In certain forms of phlebitis there is a strong tendency to recurrence. This is true of syphilitic phlebitis, of idiopathic recurrent thrombophlebitis, and of thrombo-angeitis obliterans. In syphilitic phlebitis the tendency is for the recurrence to attack different veins each time. In idiopathic recurrent thrombophlebitis the process attacks successive segments of the same vessel, usually until it has completely obliterated it.

Diagnosis.—The diagnosis of phlebitis of a superficial vein is usually a simple matter. The sudden onset with pain, the slight constitutional symptoms, and the thickened vessel with the overlying, reddened, œdematous skin leave little room for error. In some instances of thrombophlebitis there are sources of error, as described in the article on Thrombosis. Here also is to be found the discussion of thrombophlebitis of the veins of the different viscera and of the different vessels.

Prognosis.—This hangs upon the concurrence of thrombosis, and depends almost entirely upon the character and location of the thrombus. For this reason it is discussed under the head of disease associations and special form of thrombosis in the article on Thrombosis. Simple phlebitis unaccompanied by thrombosis has almost invariably a favorable outcome. The tendency of some forms to recurrence should be borne in mind in giving a prognosis.

Treatment.—This is essentially that of thrombosis; it depends on the cause and situation of the lesion, but is mainly influenced by the fact that thrombosis is usually present. In a few forms, such as syphilitic phlebitis, specific internal treatment is demanded; but, as a rule, the treatment consists of relieving the pain by general and local treatment, and putting the patient completely at rest. The excision of the inflamed area of vein, as recommended by the French school and by Moullin, may be advisable in some cases.

CHAPTER XIV.

THE DISEASES OF THE LYMPHATIC VESSELS.

By ALDRED SCOTT WARTHIN, Ph.D., M.D.

Introduction.—The diseases of the lymphatic vessels have hitherto been accorded but slight attention in works on internal medicine. In fact, in the majority no separate treatment of this subject is deemed necessary, and only passing allusions are made to pathological conditions of the thoracic duct or peripheral lymphatics in their connection with more general pictures of disease. This is due in part to the fact that the lymphatic system, having its roots in the lymph spaces of the various organs and tissues, stands in such intimate relationship to the parenchyma that pathological changes in one mean the involvement of the other, so that it becomes possible only in rare cases to separate the pathological anatomy of the smaller lymphatics from that of the organ or tissue concerned. Even in the case of the larger lymphatic channels it is rarely possible to distinguish independent pathological conditions. Inflammation, tuberculosis, or malignant disease of the thoracic duct may be wholly masked by the septicemia or pyemia, general miliary tuberculosis, or metastases dependent upon these conditions. To such an extent is this true that some writers have denied to affections of the lymphatic vessels any independent symptomatology aside from that resulting from obstruction to the outflow of lymph, such as œdema, chyluria, chylous ascites, chylothorax, chylopericardium, etc. As it is, many of these cases are relegated to surgery for final consideration, and for this reason the pathology of the lymphatics has been more adequately treated in surgical works than in those of internal medicine. With careful analysis the diseases of the lymphatics must come to hold a more independent and important position. This is true particularly of the thoracic duct and its branches.

1. DISEASES OF THE THORACIC DUCT.

General Considerations.—The thoracic duct is the main trunk of the lymphatic vascular system, and receives the chief portion of the lymph from the peripheral lymphatics. It is formed by the union of the lumbar lymphatic trunks (*trunci lumbales*), that convey the lymph from the lower extremities, pelvis, genitalia, and abdominal wall, with the intestinal trunk (*truncus intestinalis*), into which the chyle vessels empty. At the point of union at the level of the first or second lumbar vertebra a dilatation is usually found (*receptaculum* or *cisterna chyli*). This sac, however, is not always present, and its place may be taken by a plexus of lymphatic vessels. Passing through the aortic opening in the diaphragm, the duct ascends in the posterior mediastinum to the right of the median line,

lying between the aorta and right vena azygos. At the level of the fourth dorsal vertebra it turns to the left and ascends on the M. longus colli to about the height of the sixth cervical, and, after receiving the lymph trunks from the upper portion of the body, empties into the left subclavian vein just before its union with the left internal jugular.

The routine examination of the thoracic duct in autopsy work has been much neglected, owing to the prevalent mistaken idea that its demonstration is a matter of great difficulty. As a matter of fact, it is easily found. If, after the removal of the heart and left lung, the right lung is turned over into the left side of the thorax, and the tissues on the right side of the posterior mediastinum and the overlying pleura are put on the stretch, it is but rarely that some portion of the duct is not recognized through the delicate pleural covering or as soon as the latter has been slit longitudinally and dissected away. The greater portion of the duct can be dissected out at this time, or a thread may be tied around it to make its recognition more easy after the removal of the neck organs and thoracic vessels.

The right lymphatic duct, sometimes called the right thoracic duct, receives the lymph from the right side of the head, neck, thorax, right lung, right heart, right upper extremity, and upper surface of the liver. It is less than an inch long and empties into the right subclavian or internal jugular near their junction. Like the thoracic duct its opening has a double valve. Nothing is known of its pathology.

Anomalies.—Numerous anomalies have been described. Instead of a single duct there may be a plexus of small lymphatics extending along the entire course of the normal vessel, or the duct may be represented by two or more distinct trunks, which may run an individual course or may re-unite to form a single channel, persisting throughout the remaining portion of the course or again dividing. In the case of a double duct, one vessel may empty into the right subclavian vein, the other one into the left, or the termination may consist of a delta-like lymph plexus. Anomalies of termination are very frequent. The duct may empty into the right subclavian vein, right internal jugular, by two trunks into the right and left subclavians or the right and left internal jugulars, the junction of subclavian and internal jugular on one or both sides, the brachiocephalic vein, inferior vena cava, azygos major, etc. In the case of termination by plexus, the various trunks may empty into several different veins. Some of these anomalies of termination occur so often that they have been regarded as representing normal variations.

The clinical significance of these anomalies is chiefly surgical. The anomalous branches may be injured by surgical procedures, particularly when the duct or ducts rise high in the neck. This occurs not infrequently in the case of a right-sided duct or a double duct. Lymph fistula or chylothorax constitutes the usual symptom. In other cases the anomalous duct or branch may be ruptured by trauma and the resulting chylothorax be regarded as a medical condition until its nature is discovered.

Absence of the thoracic duct is mentioned repeatedly in obstetrical literature as a cause of *œdema neonatorum*, but authentic observations of such an anomaly are apparently wanting.

Hemorrhage.—Hemorrhage into the thoracic duct may occur as the result of trauma to the mesentery or intestines, retroperitoneal or mesenteric hemorrhages due to congenital or acquired hemophilia (severe anemia, chronic icterus), extreme passive congestion of the portal system in hepatic cirrhosis, ruptured sac in ectopic gestation, and following pelvic operations. The entrance into the general circulation through the thoracic duct of a large amount of blood so changed would offer conditions favoring thrombosis and embolism in the smaller vessels of the body. No symptoms referable to a thoracic duct condition would exist unless thrombosis occurred within the duct itself or at its mouth, obstructing it so that chylothorax or chylous ascites would occur in the absence of an adequate collateral circulation. Such cases have not yet been recognized.

Thrombosis.—Thrombosis of the thoracic duct has been observed in a number of cases. Two varieties may be described. In one the thrombus begins within the subclavian vein, at or near the mouth of the duct, and finally obstructs the latter; in the other form the thrombus occurs primarily within the lumen of the duct. The cases described by Oppolzer, Cayley, Turney, and others belong probably to the first type. Oppolzer's case was one of cardiac valvular lesion. At autopsy a thrombus obstructing the mouth of the thoracic duct was found. There was neither chylothorax nor chylous ascites present. Cayley's case presented a thrombus closing the mouth of the duct and causing such marked dilatation of the duct and the receptaculum chyli with its radicles, that the latter could be felt as a large tumor during life. In Turney's case both chylothorax and chylous ascites were present, the duct and all its radicles being dilated, while its mouth was blocked with a thrombus.

Etiology.—The causes of thoracic duct thrombosis have been given by various authors as hemorrhage into the duct, inflammation of its wall, trauma, tuberculosis, metastasis of malignant tumors, infection, presence of filariæ, pressure of neighboring tumors, aneurisms, anomalous vessels and exostoses of the vertebræ, the obliteration of the left subclavian vein, etc. Those occurring primarily in the vein at the mouth of the duct may be dependent upon a valvular lesion, or they may be infective. Carcinomatous thrombi may also have their seat at the mouth of the duct. There can be but little doubt that some of the so-called thrombi found within the thoracic duct were tubercles or tumor-masses.

Symptoms.—The symptomatology is purely one of obstruction in so far as its distinctive features are concerned. Chylous ascites alone or combined with chylothorax or chyluria would point to such an obstruction. The dilated receptaculum might be palpable through the abdominal wall as an elastic retroperitoneal tumor. Aspiration of such a tumor should be practised, as it might lead to a definite diagnosis of obstruction of the duct from the character of the fluid obtained. Obscure abdominal pains, intestinal disturbances, œdema or elephantiasis of the external genitals or lower extremities may occur as features of the clinical picture.

The occurrence of symptoms of obstruction, as well as their severity, will depend upon the adequacy of the collateral circulation. A thrombus located at the mouth of the duct is more likely to cause obstruction to

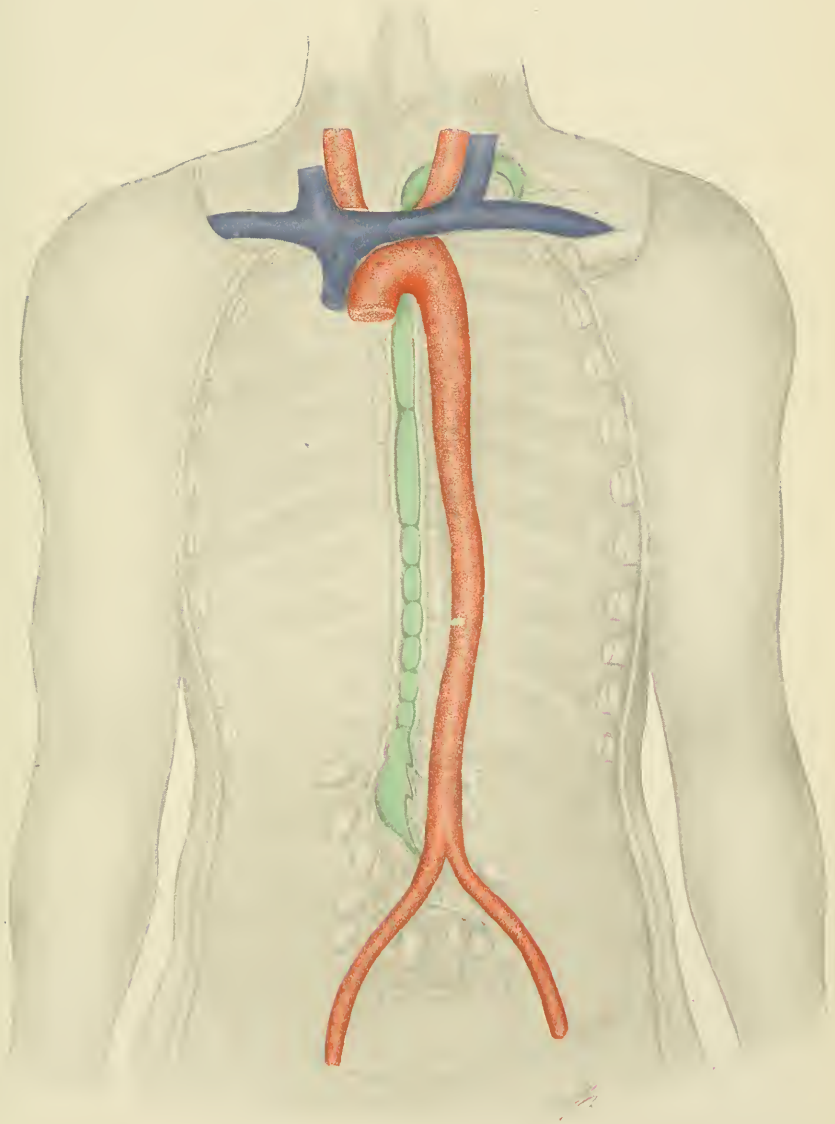
the lymph outflow than one located nearer to the receptaculum; but, even in the former case, an anomalous termination may be able to compensate fully, and symptoms of obstruction may be wholly wanting. A thrombus slowly formed, or one that only partly blocks the lumen, is not likely to cause any symptoms of obstruction.

The thrombus may undergo simple softening, and finally disappear entirely. One case, at least, has been reported of the organization of the thrombus and the permanent obstruction of the lumen of the duct by a mass of newly formed connective tissue canalized by new blood and lymph vessels. Calcification of the thrombus may take place, leading to the formation of a thoracic duct stone. The "*chyle stone*" occurring in the receptaculum, described by Scherb in 1729, is an interesting finding, and probably represents an old calcified thrombus.

Fat Embolism.—In 1910 Wilms recommended the establishment of a thoracic duct fistula in the treatment of fatty embolism, on the ground that more fat is added to that in the blood by absorption through the lymphatics, the fat passing the lymph nodes and reaching the thoracic duct, whence it passes into the venous circulation some time after the fat that gained immediate entrance into the veins. This accession of fat may be the final straw in bringing about the fatal termination, and if this increase in the fat in the blood stream can be prevented the patient may survive. Wilms carried out this operation on one case of fatty embolism in a patient who fell from a window and sixteen to twenty hours after the operation became soporific, his temperature rising to 104° F., respirations to 40. Believing the entrance of the fat to be chiefly through the lymphatics, Wilms opened and drained the thoracic duct, large fat-droplets appearing in the lymph. The fistula closed on the ninth day, the patient recovering gradually. Wilms' method was used experimentally by Fritzsche (1910), who found that drainage of the thoracic duct warded off a fatal termination when the operation was performed at the first signs of danger. The risk of the operation is slight, and the consequences negligible. On the other hand, as so few patients with fatty embolism diagnosed *intra vitam* survive, the risk of the operation is nothing compared to that of the condition itself. As Grondahl says, this method of treatment is certainly theoretically a good one, and surgeons should be urged to carry it out whenever there are indications of cerebral fatty embolism.

Inflammation.—A number of cases have been described; in the majority it has been purely secondary to inflammatory processes involving the chyle vessels and the pelvic radicles. In dysentery, suppuration of the mesenteric glands, pelvic suppurative processes, etc., the entrance of bacteria into the mesenteric and pelvic lymphatics is probably the rule, but in the majority of cases they appear to pass on with the lymph into the blood stream without causing local lesions in the duct or its radicles. It is not improbable that the thoracic duct becomes the most important portal of entrance into the blood stream of pyogenic organisms coming from local lesions in the territory drained by it. It plays, therefore, a very important rôle in the causation of pyemia and septicemia. The metastatic abscesses occurring in dysentery may well owe their origin to

PLATE VIII



Acute Primary Suppurative Inflammation of the Thoracic Duct. (De Forest.)

(Bacillus pyocyaneus.)

a transportation through the thoracic duct. Likewise, the entrance of gonococci into the blood stream may occur chiefly through the thoracic duct, as it is now known that the gonococci gain entrance to the lymphatics of the genitals and pelvis. In some cases the walls of the duct may become the seat of a purulent inflammation, and at autopsy the lumen may be found to contain pus. The independent nature of the thoracic duct suppuration is not clear in these cases.

In a case of purulent salpingitis in a young girl convalescing from smallpox seen by the writer, the pelvic and mesenteric lymphatics were the seat of a marked suppurative inflammation, the receptaculum and the thoracic duct being similarly involved. All the organs contained pyemic abscesses. Aside from the high leukocytosis (70,000), there were no symptoms that could be connected with the thoracic duct involvement.

Few observations exist of independent inflammation of the duct. Enzmann gives 6 cases as representing this condition, but the evidence is unsatisfactory. De Forest[1] has reported at length a case of *purulent inflammation of the duct*, apparently primary in character. The patient, who had shortly before had an attack of "ptomaine poisoning," became ill after partaking heartily of "cold-storage poultry," and developed nausea, followed by chills and fever, passing finally into a condition resembling typhoid fever, death taking place on the twenty-fourth day. At autopsy no evidences of typhoid fever were found, but the thoracic duct was distended to the size of a bologna sausage and filled with foul pus of a bluish-color. (See Plate VIII.) The constrictions at the valves gave it a peculiar sacculated appearance. Pressure upon the duct caused pus to trickle slowly through the terminal valve into the vein. The mesenteric glands, particularly those near the duct, were enlarged. No primary purulent process was found in the intestine or elsewhere, and there were no metastatic abscesses. Cultures were not made, but from the character of the pus the *B. pyocyaneus* was supposed to be present.

The clinical symptoms of this interesting case were those of a septicemia, passing into a typhoidal state. The positive evidences of typhoid fever were lacking; and two symptoms were present that in the light of the autopsy findings might be regarded as pathognomonic. The extremely high leukocytosis, the white cells before death reaching nearly 200,000, and the rather unusual production of nausea whenever the patient was turned upon his side were the only clinical features that can be taken to form a basis for a differential diagnosis. The sausage-like tumor might possibly have been felt by deep palpation. Otherwise the clinical picture appears to be that of a septicemia of unknown origin.

It is probable that the condition described in 1831 by Nochher as a "gangrenous thoracic duct," which was found at autopsy a few hours after death in a patient dying of a "malignant epidemic fever," may have been similar to De Forest's case. Other cases of the same nature may exist and go unrecognized, either through the failure to perform an autopsy or because of an incomplete examination. The clinical diagnosis

[1] *New York State Journal of Medicine*, September, 1907.

of such a condition has never been made up to the present time. In the case of a septicemia or toxemia of unknown origin, a progressively increasing leukocytosis up to very high counts might direct suspicion toward the thoracic duct as the seat of a purulent inflammation. The symptom of nausea mentioned above may be found to have some worth. Deep palpation with the patient in a warm bath should be tried. In the case of a localized abscess, involving some portion of the duct, the symptom of chylothorax or chylous ascites may be added. Finally, an exploratory operation might settle the matter and serve as a therapeutic measure in those cases in which the receptaculum or the abdominal portion is involved.

Chronic inflammation of the thoracic duct has been described in the literature. Andral mentions a constriction of the lumen of the duct by a formation of scar-tissue in its wall at the level of the fifth dorsal vertebra. Heller found in a woman, fifty-six years old, who had suffered from ascites and marked œdema of the pelvic tissues, that the wall of the duct was greatly thickened and its lumen almost obliterated. He regarded the condition as the result of a chronic inflammation of the wall of the duct. Other similar cases of supposed chronic lymphangioitis of the duct have been reported, but it is clear from the descriptions that the condition was one of tuberculosis or infiltration of the wall of the duct by a malignant neoplasm. Thus the case reported by Schweninger, of *lymphangioitis proliferans* of the duct was undoubtedly one of carcinomatous infiltration. Likewise, the classical cases of Cheston and Assalini, in which the duct was filled with bony masses, have been passed along in the literature under the terms "calcification," "ossification," and "*lymphangioitis ossificans*" of the duct. Certainly, the description given by Cheston leaves no doubt that the duct had been invaded by an osteosarcoma primary in the pelvis. Inflammation of the thoracic duct due to syphilis, parasites (*filaria*), etc., is hinted at in the literature, but without actual pathological demonstration.

Tuberculosis.—The thoracic duct is the most important channel by which great numbers of tubercle bacilli are rapidly disseminated throughout the body, and it, therefore, is the chief avenue concerned in the production of acute general miliary tuberculosis. The duct itself may be the seat of tuberculous lesions, from which the bacilli are carried in great numbers by the lymph into the general circulation; or the duct, while in itself not affected, may be the avenue through which great numbers of tubercle bacilli, given off from a tuberculous lymph node, may pass with the lymph into the blood stream. Further, a subacute or even chronic tuberculosis may result when a small caseous tubercle occurs in the duct, giving off from time to time into the lymph stream a small number of bacilli. The more carefully this condition is studied at autopsy the higher the percentage of thoracic duct lesions discovered. In a series reported by Longcope the duct was affected or contained tubercle bacilli in over 79 per cent. of cases of acute miliary tuberculosis. Whipple reported a series of cases in which smears from the contents of the duct showed tubercle bacilli in all cases in which the mesenteric glands were involved. Tuberculosis of the thoracic duct cannot be

regarded as rare, and its relation to general miliary tuberculosis is more important than tuberculosis of veins and arteries. Further, both clinical and experimental evidence shows that tubercle bacilli may pass into the thoracic duct through an intestinal wall showing no tuberculous lesions.

The infection of the duct takes place usually from caseous mesenteric, retroperitoneal, or mediastinal lymph glands, although it is possible that in some cases tubercle bacilli pass through the intestinal wall without causing lesions and into the lymphatics to excite first within the thoracic duct the characteristic lesions of the disease. Ordinarily, however, the thoracic duct lesion is secondary to an older tubercle of a lymph node. In cases of endothoracic tuberculosis a retrograde metastasis into the paraortic lymph nodes of the abdomen is frequently seen.

The character of the lesion within the duct may vary greatly. There may be scattered miliary or submiliary nodules, multiple or single in the intima of the duct, or the entire wall may be studded with larger conglomerated polypoid tubercles. Caseous ulcers may be present, particularly upon the valves. In many cases there is a single large caseous nodule near the upper end of the duct, but sometimes in or near the receptaculum. In advanced cases the wall of the duct throughout its entire length may be thickened and caseous, the lumen in part obliterated or in part varicose, and in the latter case filled with a caseous or whey-like substance. Tubercles forming behind a valve flap push the flap out into the lumen, and so obstruct the latter. Chylous ascites and chylothorax may result from tuberculous obstruction of the duct, but this is rare, an adequate collateral lymph circulation usually being developed. Except for such symptoms of lymphatic obstruction, tuberculosis of the duct gives rise to no definite clinical picture.

Syphilis.—Gummatous lesions of the thoracic duct or lesions of other nature definitely ascribable to syphilis have apparently not yet been observed. In congenital syphilis great numbers of spirochetes may be present in the wall of the thoracic duct without the occurrence of recognizable histological changes.

Ectasia.—Dilatations of the thoracic duct are not uncommon. They have been reported in the literature under various heads—aneurism, varicosity, cysts, etc. The duct may be dilated as a whole or in part. The nature of some of these localized dilatations is not at all clear. In part they appear to be the result of obstruction, either from within (thrombus, tubercle, carcinoma) or from external pressure upon the duct (tumor, aneurism, etc.). When the obstruction occurs at the upper end the entire duct may be dilated, presenting sausage-like sacculations, while the receptaculum is as large as a hen's egg, or even larger. In other cases no obstruction is present, and there is no evidence of pressure from within or without. On the other hand, in many cases where there is actual obstruction of the duct, no dilatation of the duct occurs. By some writers the cause of the partial dilatations or varicosities occurring without obstruction is sought in a local weakening of the wall of the duct, due to defective development or to atrophy.

There is no symptomology, or, in the event of rupture or obstruction, an associated chylothorax, or chylous ascites or chyluria, calls attention

to the thoracic duct. The cystic enlargement of the receptaculum may be seen or palpated as a fluctuating retroperitoneal tumor, the contents of which may be recognized on aspiration.

Chyle Cysts.—The cystic dilatations of the radicles of the thoracic duct deserve special mention. They may occur as the result of obstruction to the duct or of its branches, as the result of local inflammation, or partake more of the nature of tumors. They are classed by different writers partly as *lymph cysts* and partly as *cystic lymphangiomata* or *chyle angiomata*. They may be solitary or the peritoneum may be studded with them. They vary in size from that of a pea to a man's head, are often pedicled or clustered like a bunch of grapes, and usually possess very delicate, thin walls. Their contents are whitish, creamy, or, more rarely, caseous. In the large ones the fluid may be clear and several liters may be present. In cases of chyle stasis the entire peritoneum is sometimes dotted with small whitish points, corresponding to small dilatations of the chyle vessels. The intestinal folds and villi may also be studded with them. When lying close together the appearance presented is that of a lymphangioma. Small, isolated chyle cysts of this type are not at all uncommon, and are probably due to some local obstruction of a chyle radicle. The multiple lymph cysts are usually associated with a chronic peritonitis. The larger tumors are more rare and are apparently independent of inflammatory changes. They may be found even in children, and are probably to be classed with the tumors. They usually lie behind the stomach or an intestinal coil, the percussion tone over them often being tympanitic. In some cases the stomach or intestine may be pressed so closely against the abdominal wall that only a dull percussion note is obtained and the compressed stomach or intestine may be injured by aspiration or operation. The points of differential diagnosis are: the presence of a fluctuating retroperitoneal tumor, its location and relations, the character of the fluid obtained by aspiration, etc. The symptoms are wholly those of pressure.

Obstruction.—This may be caused by thrombosis, tuberculosis, metastatic tumors, inflammation, parasites within the duct, compression of the duct by diseased lymph glands, aneurism, neoplasm, exostoses and scar tissue, inflammatory constrictions of the duct, thrombosis of the subclavian or innominate vein, high venous pressure in cases of tricuspid insufficiency, etc. The effects vary greatly in different cases; when in the lower part of the duct an adequate collateral circulation is usually established without much damage resulting. Even with an obstruction of the terminal portion of the duct some cases may present no symptoms. In all cases in which the collateral circulation is inadequate there results a chyle stasis, with dilatation of the duct and its radicles. The chyle may escape from the distended vessels by transudation or rupture, and may infiltrate the tissues or collect in the serous cavities, giving rise to a chylothorax, chylopericardium, or a chylous ascites.

Rupture.—The thoracic duct may be torn or ruptured through trauma or surgical operation, or as the result of distension following obstruction, erosion by aneurism or tumors, etc. The deep situation of the duct protects it from trauma, but laceration has followed shot and stab

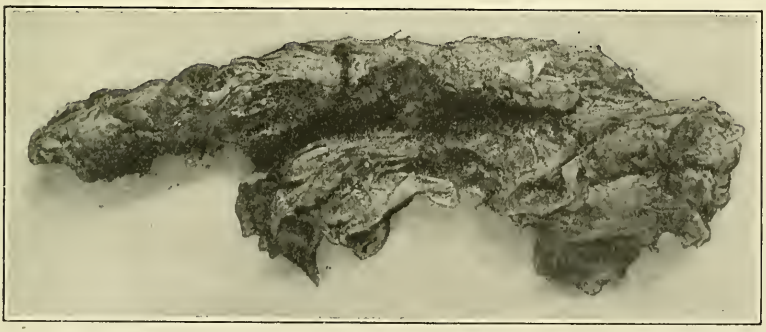
wounds, fracture of a rib, severe straining or coughing, severe blows upon the abdomen, crushing of the thorax or abdomen, etc. In operations upon the cervical region the duct may be wounded, particularly when the duct runs high into the neck. The removal of the lower cervical lymph glands and the complete operation for removal of carcinoma of the breast are the operations most frequently followed by evidences of injury to the thoracic duct. The injury may be noticed at the time of operation or not until the dressing of the wound. There may be a distinct gush of milky or serous fluid, or such a fluid may slowly collect in the wound or dressings. In the case of an internal rupture, the condition is revealed through the development of chylothorax or chylous ascites.

The rupture of the duct is fatal in some cases, as the result of a rapidly developing marasmus following the loss of large quantities of chyle. Some cases heal spontaneously. Others recover after packing of the wound or ligation or suturing of the duct.

Tumors.—Primary tumors of the thoracic duct have not yet been observed. Secondary tumors, particularly carcinoma, are not infrequent, and there can be but little doubt that in the generalization of carcinomata located primarily in the abdomen or pelvis the thoracic duct plays as important a rôle as that performed by it in the dissemination of tuberculosis. In the case of such transportation of carcinoma cells the duct may remain free itself, or may contain thrombi or tumor cells, or its walls may present carcinomatous infiltration.

Mature Connective-tissue Tumors.—No positive demonstration of the occurrence of these in the walls of the duct has yet been given. The *osteomas* and *chondromas* found metastatic in the duct were undoubtedly sarcomatous in nature. The *cystic* or *cavernous chylangiomas* or *lymphangiomas* have been mentioned above under Cysts.

FIG. 51



Lymphosarcoma of receptaculum chyli and thoracic duct, seen from behind. Case of chylous ascites and chylothorax.

Sarcoma.—But few cases of metastatic sarcoma of the thoracic duct have been reported, and there exists no authentic observation of any primary sarcoma of its walls. The writer has seen two cases of metastatic sarcoma in the thoracic duct. In one case there was a sarcomatous teratoma of the testis, and in the receptaculum chyli a

sarcomatous nodule completely occluding its lumen was found. Chylous ascites was not present. In the second case (reported by Dock[1]) chylous ascites and chylothorax were present in a case of *lymphocytoma* (*lymphosarcoma*) with lymphocythemic blood, although the total number of the white cells was not greatly increased. Occupying the root of the mesentery a large nodular lymphoid tumor was found sending up into the thoracic duct a solid cord of tumor tissue completely filling its lumen and projecting above into the left subclavian vein (Fig. 51). The walls of the duct were in part adherent to the mass and infiltrated with tumor cells. A case much resembling this one was reported by Herzog in 1899.

Primary *endothelioma* of the peritoneum reaches the thorax through the thoracic duct and involves the walls of the latter.

From the few reports in the literature it would seem that secondary sarcoma of the thoracic duct is most likely to occur in cases of primary sarcomatous tumors of the testis, lymphocytoma of the mesentery, osteo- or chondrosarcoma of the pelvic bones, and primary endothelioma of the peritoneum.

Carcinoma.—Secondary carcinoma of the thoracic duct is not infrequent, and a fairly large number of cases has been reported since the first one seen by Astley Cooper in 1798. Schwedenberg has pointed out the great importance of the thoracic duct as the chief channel by which carcinoma cells pass from the abdominal and pelvic organs into the lungs and the systemic circulation. Actual tumor development within the duct or in its walls is not a necessary feature of such a transportation; it may occur without any involvement of the duct itself.

Of the 26 cases of secondary carcinoma of the duct collected by Winkler, the primary growth was in the stomach in 10 cases, in the uterus in 8, gall-bladder in 3, and 1 each in the testis, pharynx, ovary, adrenal, and kidney. In all of these cases secondary nodules were present in the mesenteric or retroperitoneal glands. In the 12 cases reported by Schwedenberg 4 cases were primary in the uterus, 3 in the stomach, 2 in the rectum, and 1 each in the kidney, colon, and mamma. In the last case the duct was involved through retrograde metastasis.

The appearance of the duct when it is the seat of secondary carcinoma varies greatly. To the naked eye there may be no evidence of the presence of tumor cells. Small nodules, barely palpable, may be present in the wall, or the lumen of the duct may be closed by larger masses. At other times the duct may be of the size of a finger throughout its entire length, and completely filled with tumor masses. A sacculated appearance is produced by the growth of nodules behind the valves. The lumen may be completely or partially obstructed, or the cancer mass within the lumen may be recanalized. In some cases the tumor mass is larger in the receptaculum and tapers off above. The lymph glands lying along the thoracic duct may contain secondaries when the duct itself shows no involvement, and, macroscopically, it may be difficult to say whether the latter is carcinomatous or not. The enlarged chain of lymph glands should not be mistaken for a diseased duct.

[1] *Amer. Jour. Med. Sci.*, 1907, cxxxiv, 634.

Microscopically the duct may be found to contain free carcinoma cells or masses of these. In the majority of cases thrombi are associated with the latter, and such carcinomatous thrombi are usually situated behind the valve. They are also found at the point where the duct crosses the aorta. With the growth of the tumor cells the thrombus may become organized and adherent to the vessel wall. The latter, in turn, becomes infiltrated with the tumor cells, and the inflammatory reaction dependent upon this appears as a diffuse thickening of the wall of the duct (endolymphangitis carcinomatosa). Such an inflammation and tumor infiltration may extend from the duct into the subclavian vein.

The only symptoms of secondary malignant disease of the thoracic duct that can be recognized clinically are the results of the obstruction of the duct, viz., chylothorax, chyluria, or chylous ascites. The occurrence of these conditions is dependent, however, wholly upon the inability of the collaterals to take care of the lymph stasis, and in the case of an abundant anastomosis they may be absent. The tumor masses in the receptaculum chyli may reach such a size that they can be palpated. Enlargement of the left supraclavicular lymph nodes in connection with an abdominal or pelvic tumor is an important diagnostic sign of carcinoma metastases through the thoracic duct.

Parasites.—Cysticerci and filariæ may occur within the thoracic duct and obstruct its lumen, giving rise in some cases to chylothorax and chylous ascites, but more often to chyluria. Thrombosis of the duct may occur as the result of the presence of the parasites and the inflammatory changes set up by them in the wall of the duct.

Symptoms and Diagnosis of Thoracic Duct Disease.—A cystic fluctuating retroperitoneal tumor, containing chyle, as shown by aspiration, and located in the region of the receptaculum chyli, points to a dilatation or cyst of the duct or its radicles. Symptoms of sepsis or pyemia, with a very high leukocytosis and an elongated tumor palpable in the region of the receptaculum chyli, indicate a purulent inflammation of the duct.

Chylothorax and chylous ascites are the cardinal signs of an obstruction or rupture of the duct. Chylopericardium, chyluria, œdema of the pelvic tissues and genitalia may be associated with the other two.

Chylous Ascites.—Milky or opalescent fluids are not infrequently seen in cases of ascites. Some of these correspond so closely to chyle in their physical and chemical qualities that one has no hesitation in applying to them the term *chylous*. In other cases the lactescent fluid has been found to differ somewhat from chyle, and to such the term *chyliform* has been applied. Still more rarely—in fact but one case of the kind has been reported—a milky fluid containing neither fat nor granules occurs, a *lactescent, non-chylous* effusion. Since the character of the last named could easily be ascertained by examination, the diagnostic problem of chief importance is the distinction between chylous and chyliform fluids. Some writers believe that such a differential diagnosis cannot be made from the physical and chemical characteristics, since fluid in all respects resembling chyle is found in pathological conditions of the peritoneum in which no lesion or obstruction of the thoracic duct can be ascertained. Various authors also hold that the only distinction

between *chylous* and *chyliform* fluids is one of dilution or mixture, in the latter case with serous fluids of inflammatory origin. According to some, the term chylous should be used only when a definite lesion can be found in the lymphatics; in chyliform or adipose ascites, the lymphatics must present no abnormalities of any kind. The question demands some criterion by which a chylous fluid may be told from a chyliform effusion in which the milkiness is due to the presence in a serous fluid of endothelial, pus, or tumor cells undergoing or having undergone fatty degeneration. Such fluids have been found in peritoneal tuberculosis, carcinoma, sarcoma, hepatic cirrhosis, cardiac lesions, chronic peritonitis, lipemia, etc.

The character of the fluid will decide promptly in some cases. If it is white, with numerous fat-droplets present, and forming a creamy layer on standing, and if, in addition, it contains more than 0.02 of sugar, the fluid may safely be regarded as chylous and as coming from the lymphatics. The microscopic examination of the sediment may in some cases reveal the cellular origin of the fat, but usually no trace of the cells can be seen. The absence of conditions favoring the formation of a chyliform or adipose ascites adds to the strength of a conclusion as to its chylous nature.

Cases arise, however, in which there is great difficulty in deciding whether to call an effusion chylous or chyliform. A large amount of fat and a relatively high percentage of sugar may be found in chyliform effusions when no lesions of the thoracic duct or chyle vessels can be demonstrated. It is possible that some of these fluids resembling chyle were in reality a diluted chyle, and it is highly probable that a diapedesis of chyle may take place into the peritoneal cavity through the walls of distended chyle vessels without any actual rupture.

If chylothorax is present also, the probabilities of a thoracic duct lesion are made much greater. The sudden development of anorexia, anemia, and emaciation are also regarded as symptoms favoring the existence of obstruction or a rupture of the duct. If the chylous fluid returns quickly after its removal by tapping, the probabilities are that a chyle fistula is present. In spite of these distinctions, cases of milky ascites apparently occur in which, even at autopsy, it has been impossible to say whether the effusion was chylous or chyliform.

Chylothorax.—The same difficulty exists in the case of a milky fluid in the pleural cavity, and the two forms, chylous and chyliform effusions, are likewise distinguished here. The former occurs in the event of distended or ruptured lymphatics; the latter is found in the case of the fatty degeneration of tumor, pus, or endothelial cells, in secondary carcinoma of the pleura, tuberculous and non-tuberculous pleuritis, pulmonary abscess, lipemia (?), etc. It is a relatively rare condition, and the majority of cases of lactescent pleural effusion are instances of chylothorax, and point to lesions of the thoracic duct. The same differential points hold good as for chylous ascites.

Chylopericardium.—Milky effusions into the pericardial sac are still more rare. Both chylous and chyliform fluids have been described; in one case the chylous fluid came from the rupture of a lymph vessel, in

another the chyliform fluid was regarded as a transudation from a chyliform effusion in the left pleural cavity. The significance of chylopericardium in thoracic duct disease is that of chylous ascites.

Chyluria.—The presence of emulsified fat and albumin in the urine gives it the appearance of chyle. Sugar is but rarely present. The appearance of chylous urine is very characteristic; it closely resembles milk, but usually contains pinkish coagula. Sometimes the entire urine coagulates on standing, or it separates into an upper creamy layer and a lower bloody stratum. Chyluria may be brought about by any obstruction to the thoracic duct, whether due to thrombosis, tumor metastases, tuberculosis, external pressure, filariæ, etc. By far the most common cause of chyluria is the obstruction of the duct by either the adult or embryonic form of *Filaria*. In northern latitudes chyluria occurring in individuals who have not been in tropical or subtropical countries is due to some other form of obstruction of the duct.

As a symptom chyluria is usually intermittent, being dependent upon the position of the body, character of the food, digestion, amount of fluid taken, exercise, etc. In rare cases chyluria may appear during childbirth and gradually cease after delivery, to return again during the next parturition. Such cases may be explained as due to temporary lymph stasis. Symptoms of pain in the back, groin, perineum, or testicles may accompany or precede the appearance of the chyle in the urine. When the chyluria persists over a long period of time the patient may become greatly anemic and emaciated, and finally die of exhaustion.

Serous or chylous œdema of the pelvic tissues, abdominal wall, genitalia, legs, etc., *lymph scrotum*, *lymphocele*, *chylocele*, *elephantiasis*, etc., are also conditions pointing to obstruction of the thoracic duct.

Prognosis.—This is dependent wholly upon the nature of the obstruction. It is favorable only in those cases in which the cause can be removed, or, the cause being non-malignant, the lymphatic circulation can again be restored through recanalization of a thrombus, establishment of adequate collaterals, etc. Filarial obstruction is rarely cured, but the patient may live many years in spite of it, unless the amount of chyle lost is very great and the drain persistent.

Rupture of the thoracic duct in the cervical region is given a good prognosis, as the wound may heal spontaneously or surgical treatment result successfully. Spontaneous healing of rupture of the duct in the thoracic or abdominal cavities also takes place. In some cases, in spite of surgical treatment, the patient rapidly becomes emaciated and dies from exhaustion. In general, it may be said that the prognosis in cases of thoracic duct disease with symptoms of obstruction is grave.

Treatment.—The physician's part in the treatment of disease of the thoracic duct is largely confined to symptomatic measures. His function is in the majority of cases the diagnosis of the condition and the preparation of the patient for the surgeon, in case he considers surgical interference justifiable. Beyond the first diagnostic aspiration, tapping should not be carried out except as a final necessity, since the loss of large quantities of chyle weakens the patient. Peritoneal absorption of the effusion should be permitted as much as possible. The food should be

concentrated, and a diet easily digested and absorbed by the stomach should be advised. The amount of fluid taken should be restricted. In the majority of cases the ultimate treatment becomes surgical.

2. DISEASES OF THE SMALLER LYMPHATICS.

General Considerations.—The lymphatic capillaries consist of a simple endothelial tube. The system is believed to be wholly a closed one, and an open communication of the lymph capillaries with the so-called "tissue spaces" is now doubted by the majority of writers. The intimate relationship of the smaller lymphatics to the tissue parenchyma is such that a clinical separation of diseases of the former from those of the latter is well-nigh impossible. The larger lymphatic vessels have distinct walls, somewhat resembling those of the veins, but in the arrangement of the elastic tissue more like the smaller arteries. In the larger trunks an inner and outer elastic limiting membrane may be distinguished. The larger vessels possess numerous valves. Even in the case of the main lymphatic trunks only a limited number of conditions can be separated as independent affections. Of these, inflammation, ectasia, and tumors constitute the most important.

Lymphangitis.—*Simple acute lymphangitis* is a very common affection. It occurs most frequently in association with infected wounds of the hands or feet, and is usually due to streptococci, although staphylococci, gonococci, and pneumococci may be found at times. The bacteria either pass directly into the lymph vessel from the infected wound or invade the wall of the vessel from without. Wounds received during surgical operations or autopsies, infected "hang-nails," corns, cryptogenic infections of the hair follicles, etc., are among the most common forerunners of lymphangitis; but localized inflammation of the lymphatics independent of any primary focus of infection is far from uncommon. Such forms of lymphangitis are found particularly about the lips, nose, mouth, throat, penis, and vulva.

The majority of the above forms of lymphangitis are frankly surgical, and their thorough consideration is out of place in a work on internal medicine. Nevertheless, lymphangitis as a secondary phenomenon or complication plays a part of practical importance in general medicine. It occurs not infrequently during the course of the acute infectious diseases, particularly in scarlet fever, smallpox, measles, diphtheria, etc. It is frequently associated with herpes. In some individuals severe colds are preceded or accompanied by a localized lymphangitis of the lips or nostrils that may or may not go on to the development of herpetic lesions. Erysipelas is frequently complicated by a typical lymphangitis. Of the chronic specific infectious diseases, gonorrhœa, syphilis, and tuberculosis are especially likely to show an incidental lymphangitis, due, however, to the specific agent of infection rather than to a secondary pyogenic infection. Lymphangitis is a constant feature of bubonic plague. Other forms of lymphangitis are those arising after Röntgen irradiation, sunburn, contact with poison ivy or sumach, bites and stings of insects, etc.

Pathology.—Three forms of acute lymphangitis occur—*simple, purulent* and *proliferative.* In the simple form the wall of the lymphatic and the tissue immediately about it (perilymphangitis) are hyperemic, œdematous, infiltrated with cells, and may present small hemorrhages. The wall becomes thickened, the endothelium swells, and comes to resemble epithelium. It may become necrotic and desquamate, or it may manifest proliferative activity. Coagulation of the lymph within the vessel may occur (thrombolymphangitis), or it may remain fluid. After the cessation of the cause of the inflammation the exudate may be quickly absorbed, and with the regeneration of the damaged endothelium the normal conditions are restored. A persistence of the exciting cause may lead to a chronic process.

In the *purulent* form there is a marked thickening of the wall of the lymphatic due to a purulent infiltration. The endothelium is swollen or desquamated, and the lumen becomes filled with pus or with a fibrinopurulent mass (purulent thrombolymphangitis). The collection of pus in the lumen in the intervals between the valves gives a beaded appearance to the inflamed lymphatic. Suppuration may occur and the vessel be completely destroyed at the site of the process, so that the vessel enters into an abscess cavity. An extensive phlegmonous process may be set up in the neighboring tissues. As the result of the transportation of bacteria to the regional lymph glands, secondary abscesses are produced in the latter, and a condition of septicopyemia may result.

An acute *proliferative exudative endolymphangitis* occurs in gonorrhœa, and is usually associated with a perilymphangitis. The lymphatic vessel becomes greatly thickened and its lumen gradually obliterated by a fibroblastic proliferation of its walls. The endothelium may also proliferate. The gonococci can be demonstrated in the lymphatic vessel and in the tissues outside. Similar acute proliferative forms of lymphangitis may occur in the case of other infections, particularly in syphilis.

Symptoms.—The symptoms of acute *simple* lymphangitis are a localized area of redness and swelling, œdema, a painful feeling of tension, pain on movement, etc. The inflammation advances from the periphery, and as a new area becomes involved the one first affected loses its redness and swelling. When a large lymphatic trunk is involved the course of the vessel is shown by a wavy red line extending up the limb, slightly elevated above the surface, having a slightly beaded, cord-like feel, and very painful on pressure. In severe cases the line of inflammation may be an inch or so broad; in slight cases the red lines are very narrow. When the deep lymphatic vessels are alone involved the only sign present may be that of tenderness on deep pressure. The lymph glands are swollen and painful, and the portion of the limb below the seat of inflammation may become œdematous. A varying degree of fever accompanies simple lymphangitis.

In the case of *purulent* lymphangitis the local and general symptoms are much more severe. The reddened cord-like swelling is more marked and more distinctly beaded. Pressure is much more painful. Small abscesses may form along the vessel as well as in the regional lymph glands, or the entire lymphatic may suppurate. An extensive phleg-

monous infiltration may then result, or a large abscess cavity may be formed. Extensive œdema of the region drained by the affected lymphatic may develop. The general condition is worse, the fever is usually high, the pain severe, and there is marked prostration. Chills and sweating may alternate in the early stages. The final picture is often that of a septicopyemia.

The chief symptoms of the *proliferative* form of lymphangitis are the thickening of the lymphatics and the development of a marked local œdema. Otherwise the clinical picture is similar to that of the other forms, although the general symptoms are usually less severe.

Diagnosis.—Lymphangitis must be distinguished from phlebitis. The general symptoms are alike, but in phlebitis the thrombosed vein when palpable is felt as a larger and deeper-seated cord, less painful on pressure. The skin is but slightly reddened or not at all, the regional lymph glands are rarely involved, while the pain is less and the fever not so high.

Prognosis.—The simple form usually recovers in a short time, the length of the course of the affection depending upon the general condition of the patient. Recovery is delayed in cachectic and enfeebled patients. In the purulent form the prognosis is graver, since the danger of pyemia or septicemia is great. After extensive suppuration of a lymphatic vessel or group of vessels a condition of chronic œdema of the region concerned may develop, and perfect recovery is not likely.

Treatment.—An evident cause of infection should be removed according to proper surgical methods. Extreme tension may be relieved by incision. In the involvement of the lymphatics of an extremity the limb should be elevated and complete rest enjoined. In the case of small, localized areas of lymphangitis hot or cold antiseptic dressings may be applied. Particularly in the case of the "sore nose" or "sore lip," coming so frequently under the physician's notice, do hot moist antiseptic compresses lessen the discomfort and apparently shorten the process. Early treatment may prevent the formation of herpes. In many of these cases, it should be remembered, the localized lymphangitis of the respiratory openings is often a forerunner to a severe catarrhal inflammation of the respiratory tract. Such cases should, therefore, be treated with a view of preventing the further extension or generalization of the infection. Patients who have the symptom of localized painful swellings of the lips or nose, either with or without herpes, should be put to bed and supporting and eliminating treatment carried out. The local application of astringent solutions rarely does any good.

Simple lymphangitis may be successfully treated by local and general methods without resorting to surgical measures, but all cases of purulent lymphangitis should be regarded as surgical affections. The general treatment of such cases consists also of supporting and eliminating measures. A liberal soft diet should be advised, the bowels should be kept open, and tonics and stimulants administered according to indications. Likewise, the degree of pain and prostration must govern the use of sedatives, hypnotics, or analgesics. Massage and various measures such as bandages, casts, hydro- and electrotherapy may be necessary after the process has subsided to combat the stiffness and œdema.

Chronic Lymphangitis.—Chronic inflammation of the lymphatics may be caused by the presence of parasites (filariæ) within the lymph vessels, chronic infections (gonorrhœa, syphilis, tuberculosis, etc.), absorption of products from neighboring ulcers or abscesses, extension of malignant tumors into the lymphatics, etc. In the lymph capillaries the endothelial cells become swollen or hypertrophic, so that in sections the vessels may resemble gland ducts or be mistaken for strands or cords of carcinoma cells. In the large lymphatics there may occur further a proliferation and induration of the connective tissue of the vessel wall and of the surrounding tissues. This may in time lead to a complete obliteration of the vessel. Pathologically there may therefore be distinguished the forms known as *endolymphangitis proliferans* or *productiva* and *lymphangitis productiva* and *fibrosa obliterans*. As the result of the obliteration of the lymph vessels a chronic œdema and elephantiasis of the region tributary to the affected vessels may develop. Productive and obliterative lymphangitis are very common in inflamed serous membranes and in the lungs. In the latter the obliteration of the lymphatics as the result of chronic inflammation plays a very important part in the production of anthracosis and in the development of later affections of the lungs, particularly in pneumonokoniosis. An obliterative lymphangitis is very common in the lymph vessels leading from a part affected by a malignant tumor, even when no extension of the growth into the lymphatics has occurred.

Only when the large lymph trunks or the superficial lymphatics are the seat of chronic inflammation are clinical symptoms evident. Chronic œdema, elephantiasis, lymphorrhagia, lymph fistula, chyluria, etc., are the most important clinical features. In the case of superficial lymphatics the thickened and indurated vessels may be felt as firm cord-like structures. The involvement of a local plexus of lymphatics may give rise to a tumor-like formation (lymphangioma circumscriptum, etc.).

Treatment.—This is concerned chiefly with the removal of the etiological factor and the improvement of the lymph stasis, œdema, or elephantiasis that may have resulted. The latter is partly surgical and in part medical. In the latter case the indications are similar to those for the treatment of acute lymphangitis.

Tuberculosis.—Secondary tuberculosis of the lymph vessels is very common, particularly in those of the mesentery and intestine. In the superficial vessels of the extremities it is more rare, and occurs usually in association with lupus or tuberculous ulcers of the hands or feet. Miliary tubercles may be found in the walls of the lymph vessels leading from the affected part, or the vessel may be diffusely enlarged, appearing as a firm, cord-like structure. Abscesses may develop along its course. In the leg a string of nodules or abscesses may be found along the saphenous vein. Tuberculous lymphangitis occurs also in the lymphatic vessels running to the axillary nodes in association with primary tuberculosis of the mamma. As the result of a retrograde metastasis within the superficial lymphatics of the thorax, tuberculous abscesses may develop in cases of mammary tuberculosis at any point in the skin of the affected side of the thorax. The axillary glands are always involved.

In the lymphatics of the mesentery and intestine a more or less marked tuberculous lymphangitis and perilymphangitis may be observed in cases of intestinal tuberculosis. The course of the lymph vessels may be shown by a tortuous string of grayish-white nodules corresponding to tubercles within or near the lymph vessels. The blocking of the vessel lumen by the tubercles or by caseous detritus may lead to a lymph stasis.

Treatment.—The local treatment of tuberculous lymphangitis is chiefly surgical. The medical treatment is of tuberculosis in general.

Syphilis.—The lymph vessels in the neighborhood of the primary sore are always the seat of a more or less marked syphilitic inflammation. In the neighborhood of secondary lesions the lymphatics are likewise involved. In the late stages a local or generalized thickening of the walls of the lymphatics may occur, and rarely gummata may be found developing within the walls of the large lymph trunks.

Lymphangiectasia.—Dilatation of the smaller peripheral lymphatics results from an obstruction or obliteration of the larger trunks when the collateral circulation is inadequate. Such an obliteration may be the result of a proliferative endolymphangitis, tuberculosis, carcinomatous infiltration of the wall of the lymph vessel, syphilis, etc., or an obstruction to the lymph flow may be due to the presence of parasites, pressure upon the lymph vessels, contraction of the surrounding tissue (perilymphangitis), removal or disease of the regional lymph glands, etc. In the superficial lymphatics ectasia is in the great majority of cases, if not in all, associated with or is the result of a chronic inflammation. In the mesentery dilatation of the chyle vessels is often the result of a tuberculous lymphangitis.

The smaller branches of the obstructed trunks usually show the dilatation in the most marked degree. In the mesentery the dilatation of the smaller lymphatics manifests itself in the form of localized cysts (chyle cysts) or as a more extensive varicosity of a lymph plexus. When the dilatation is marked, lymphorrhagia may occur, giving rise to *chylous ascites*. A similar condition in the lymphatics of the thorax may lead to *chylothorax*. In the skin the dilatation of the lymphatics leads to a chronic œdema of the affected area, and with this there may be associated a connective-tissue hyperplasia, giving rise to the condition known clinically as *pachydermia* or *elephantiasis lymphangiectatica* when involving an extensive area, or, when localized, appearing as a variety of *lymphangioma*.

Elephantiasis Lymphangiectatica or Lymphangitica.—Synonyms.—Pachydermia; elephantiasis Arabum; morbus herculeus; spargosis; tropical big leg; pucnemia tropica; phlegmasia Malabarica; mal de Cayenne; Barbadoes leg; sarcoma mucosum; hypersarcosis. The term elephantiasis Arabum was formerly used in a very loose way to designate a great variety of conditions in which there was a local enlargement of the tissues, particularly those of the skin. At the present time the use of the term has been narrowed to those affections of the skin and subcutaneous tissues characterized by a hyperplasia of the connective tissue, either diffuse, or localized to the bloodvessels, lymph vessels, or nerves.

A lipomatous form also occurs. The most common variety is that one involving the lymphatics, its general character being a chronic and progressive enlargement of a certain portion of the body due to a hyperplasia of the connective tissue of the skin and subcutaneous tissues, hyperplasia of the lymph vessels, chronic œdema and rarely a cellular proliferation or infiltration. It occurs as an endemic disease in the tropics and sub-tropics, and as a sporadic affection throughout the remaining regions of the globe.

FIG. 52

Acquired elephantiasis due to varicose ulcers.

Etiology.—The etiology of the lymphangitic form of elephantiasis is varied. It may appear as a *spontaneous congenital* or *inherited* condition, or it may be *acquired*. In the acquired forms of elephantiasis lymph stasis due to various etiological factors plays the most important rôle. The majority of the tropical cases are due to the presence of filaria in the lymph vessels, lymph stasis, chronic lymphangitis and chronic inflammation of the skin being produced by the presence of the parasite. The sporadic acquired cases are often the result of chronic erysipelatous or eczematous inflammations of the skin involving the lymphatic vessels. Any cause of chronic or recurring lymphangitis may lead to an elephantiasis of the affected region. Lupus, syphilis, varicose ulcers (Fig. 52), frost-bite, traumatism, etc., are among the numerous etiological factors.

The removal or destruction of the regional lymph glands may be followed by elephantiasis of the part tributary to the glands. The condition may be temporary or permanent. Chronic œdema due to thrombophlebitis may also form the basis for the development of an elephantoid condition. Congenital acquired cases have been observed, apparently due to an intra-uterine infection. The *spontaneous* forms of elephantiasis are those in which the *anlage* of the condition is apparently an intrinsic one, the disease developing slowly without any exciting cause or signs of inflammation. Such cases, even when developing in adult life, are regarded as congenital or inherited. In some instances a definite family history of inheritance of the affection is present. The disease occurs at all ages, but naturally is most frequent in adults. Males are more frequently affected in the tropics; in temperate regions the majority of the sporadic cases occur in women.

Pathology.—The legs and external genitals are most frequently involved, although the affection may occur in any superficial part of the body. Next to the lower extremities and genitals, the hand, arm, face, ears, and mammæ are involved, in frequency according to the order given. The affected parts may be hard and indurated (*elephantiasis dura*), or soft and pitting on pressure (*elephantiasis mollis*). The epidermis may be smooth (*elephantiasis glabra*), papillary or warty (*e. papillaris* or *verrucosa*), or nodular (*e. tuberosa*). The horny layer may be greatly thickened, presenting the appearances of ichthyosis. The skin may be pale, shining, and more translucent than normal, or it may be more or less pigmented (*e. fusca* or *nigra*). The natural folds of skin are greatly exaggerated and the surfaces between them are usually moist and have an offensive odor. Ulcers, abscesses, chronic eczema, secondary atrophic and degenerative changes complicate the picture. The affected parts increase greatly in bulk and weight; the scrotum may attain a weight of 100 pounds or more, while the extremities may exceed in circumference the trunk. From ulcerated surfaces a large amount of lymph may escape (*lymphorrhagia*). The fluid is often milky white. Varicose lymph vessels are sometimes seen on the surface, which may rupture and a *lymph fistula* result. This is more frequent in the lymphangiectatic form and particularly when the genitals are involved.

The microscopic examination of tissue showing the lymphangitic form of elephantiasis reveals a hyperplasia of connective tissue and lymph vessels. The new fibrous tissue may be very poor in cells, or it may resemble a cellular granulation tissue. The lymph capillaries are dilated, and there is usually marked œdema. A definite new formation of lymph vessels appears to take place and the walls of the existing lymphatics become thickened. The intermuscular connective tissue may become greatly increased and the muscles gradually destroyed. Osteomata may develop in the new-formed connective tissue, and the bones may become irregularly thickened as the result of a periostitis ossificans. Eventually, atrophy or necrosis of the bones may result. The pathological picture in all cases of lymphangitic elephantiasis is practically the same, no matter how varied the etiology.

Symptoms.—The early symptoms of elephantiasis vary greatly according to the cause. In the spontaneous forms there may be no symptoms

except the resulting deformity, and in advanced cases the secondary symptoms arising from pressure, ulceration, etc. The endemic or parasitic form (filarial elephantiasis) has a definite clinical picture of infection. The sporadic cases due to erysipelatous or eczematous inflammations affecting the lymph vessels of the skin have also a definite symptomatology according to the nature of the cutaneous condition. Chills, fever, swelling of the regional lymph glands, etc., may precede or accompany the development of the condition. When due to a chronic lymph stasis unattended by inflammatory changes, the condition develops gradually out of a chronic œdema without special symptoms.

The local discomfort may be great. In all forms of elephantiasis severe neuralgic pains may attend the enlargement of the part, but in the later stages a certain degree of anesthesia results from the destruction of the nerve trunks and endings. The deformity gives great annoyance, and the effect upon the general character and disposition may be very marked. Insanity, suicide, melancholia, etc., may result from the nervous worry. The great bulk and weight of the affected part may make the patient helpless or greatly interfere with his movements. Dislocation of the affected extremity is not infrequent, and in the later stages fractures of the bone may occur. Elephantiasis of the genitals usually leads to an interference with or a loss of the sexual function. The patient's unhappy state is increased by secondary ulcers, fissures, etc.

The condition of elephantiasis develops usually very slowly, but in some cases there is a very rapid growth, large tumors being formed in a short time. This is especially true of the sporadic cases of the vulva. Ordinarily it takes years for tumors the size of a hen's egg to form, but in some cases the tumors quickly reach a great size. Such forms are often mistaken for sarcoma.

Prognosis.—In so far as the elephantoid condition itself is concerned, the prognosis is not good except in those cases in which surgical treatment is possible. The condition itself does not shorten the patient's life, with the exception of those cases complicated by secondary infections. The chances for an improvement in the cases due to simple lymph stasis are good under appropriate treatment.

Treatment.—The sporadic cases met in temperate climates are best treated by the improvement or removal of the etiological factors. Varicose ulcers should be promptly healed; the venous outflow should be aided by position, bandages, etc. All causes of inflammation should be combated. In the case of the chronic erysipelatous or eczematous conditions of the skin, or in recurring local lymphangitis, vaccines may be prepared and used. The chronic œdema of the arm following the removal of the axillary glands may be prevented from developing into elephantiasis by the proper use of bandages, etc. Such cases often recover spontaneously after a number of months. If, by proper treatment, during this time the condition is reduced to a minimum and secondary infections prevented, the elephantoid hyperplasia may be inhibited so that with the restoration of the lymphatic circulation in the axilla the extremity resumes either wholly or in part its normal condition. The ultimate treatment of advanced cases becomes surgical. Ligation of the arteries has resulted in cures. Resection or stretching of the

sciatic nerve, removal or amputation of the affected portions are among the surgical measures advocated. The general treatment in these cases is along supporting and antiseptic lines.

Neoplasms.—Tumors arising from or composed of lymph vessels are of very frequent occurrence. They may be divided into two classes, the *lymphangiomas* and the *endotheliomas*. The first-named are benign, while the second class is in part benign and in part malignant.

Lymphangioma.—The neoplasms classed as lymphangiomas consist for the chief part of spaces lined with endothelium and containing lymph. The walls of these lymph spaces may be thick or very thin; in either case the lymph spaces themselves may be small or ectatic. These growths occur chiefly in the skin and subcutaneous tissue, but may be found also in internal organs. They may be diffuse or circumscribed, flat or nodular, and in the skin are frequently attended by a marked pigmentation of the epidermis and by an overgrowth of hair. In many cases it is impossible to say whether the condition represents an actual new formation of lymph vessels or simply a dilatation of preëxisting ones with a secondary hyperplasia of the vessel walls. Lymph stasis plays a very important role in the development of some of these lymphangiomatous conditions. Those forms in which an actual proliferation and new formation of lymph vessels occurs may be classed with the true neoplasms. The most common clinical forms of the lymphangioma are certain varieties of pigmented spots and patches, nevi, warts, moles, etc., of the skin and tongue, the diffuse cavernous lymphangiomata of the tongue and lips known as macroglossia and macrocheilia, the cystic tumors of the neck (*hygroma cysticum colli congenitum*) and the cystic lymphangiomatous tumors of the arm, trunk, mesentery, and thighs. These tumors are for the greater part congenital, and may be so large at birth as to hinder delivery.

Endotheliomas.—Neoplasms arising through the proliferation of endothelium either of the bloodvessels or lymphatic vessels may be classed as endotheliomas. Those arising from the endothelium of the lymphatics (*lymphangio-endothelioma* or *endothelioma lymphangiomatosum*) will alone be considered here. These belong histogenetically to the connective-tissue tumors; the benign forms may be classed with the typical varieties of this group, while the malignant forms are analogous to the sarcomata. In general the malignant endotheliomas are relatively less malignant than sarcomas. The very cellular endotheliomas are not necessarily malignant, since many of this nature are found in the parotid gland running clinically a perfectly benign course. On the other hand, the endotheliomas of the inner meninges are usually very malignant. Many writers deny the existence of a distinct class of endotheliomas, preferring to group these neoplasms either with the lymphangiomas, sarcomas, or even the carcinomas.

The most common clinical forms of the endothelioma are the fleshy wart (lymphangioma hypertrophicum), the endotheliomas arising from the lymph spaces of the peritoneum, pleuræ, dura mater and inner meninges, the endothelial tumors of the salivary glands, mammæ, testes, and ovaries, and more rarely those occurring in the face, mouth, uterus,

etc. In the case of the endothelial tumors of the serous membranes the growth of the endothelium in the lymph capillaries gives rise to a microscopic picture suggesting the structure of an epithelial tumor, adenoma, or carcinoma; and these neoplasms are often diagnosed as the latter. Many of the tumor forms known as psammoma and cylindroma belong to the endotheliomas. The endothelial tumors of the salivary glands show a special inclination to mucoid degeneration.

Prognosis.—In the case of the great majority of the lymphangiomas of the skin the neoplasm runs a benign course, and aside from cosmetic reasons occasions no trouble. Many of them are easily removed and do not return. In other forms, as, for example, the *lymphangioma circumscriptum* of the skin, recurrence usually takes place. Malignant change sometimes occurs, as, for instance, the not infrequent development of melanotic sarcoma in pigmented lymphangiomas of the skin. In general the endotheliomas of the salivary glands, dura mater, and skin run a relatively benign course, particularly the first named. Those of the inner meninges and serous membranes have about the same degree of malignancy as sarcomas. The endotheliomas of the mammæ, ovaries, and uterus are much less malignant than sarcoma or carcinoma of these organs, metastases being less frequent and the course longer.

Treatment.—The treatment is purely surgical. Electrolysis, Röntgen irradiation, excision, etc., are the methods advocated.

Secondary Neoplasms.—The smaller lymphatics form the chief highway by which the local spread of carcinoma takes place. The carcinoma cells break directly into the lymph capillaries, dilate them, and grow in them as solid plugs or cords of cells. The wall of the lymph vessel may become thickened, but may remain uninvolved by the cancer cells for some time. Such carcinomatous outgrowths in the lymphatics may be seen at some distance from the primary tumor, and are often regarded as metastases, whereas serial sections show their direct continuity with the primary. This is particularly true of the lymphatic vessels running from the mamma to the axillary glands; in cases of mammary cancer such vessels often appear as solid cords of tumor cells. The lymphatic capillary plexuses over an extensive area may be completely infiltrated by carcinoma in some cases, as in secondary carcinoma of the pleura or peritoneum, where the lymphatics of the entire surface may appear thickened and beaded like a rosary (*lymphangitis carcinomatosa*), and filled with carcinoma plugs.

Nevertheless, certain forms of sarcoma extend by preference through the lymphatics, as, for example, *lymphosarcoma, chondrosarcoma,* and certain sarcomas of the bones. All of the forms of sarcoma arising from *free* mesoblastic cells (chloroma, aleukemic and leukemic lymphocytoma, myeloid leukemia, etc.) extend through the lymphatics as well as through the bloodvessels. The spread of a malignant *endothelioma* is likewise largely accomplished by means of the lymph vessels.

Treatment.—This is purely surgical. The important point is the necessity of removing a large area of apparently normal tissues about the primary growth in order to get out the extensions into the neighboring lymphatics.

PART II.

DISEASES OF THE BLOOD.

CHAPTER XV.

THE GENERAL PATHOLOGY OF THE BLOOD-FORMING ORGANS.

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Preliminary Considerations.—Before discussing the diseases of the blood it is well to give some consideration to the data on which our knowledge of these diseases is founded, and some definition of the terms employed. The data referred to are: (1) accumulated knowledge regarding blood formation in embryonic and postnatal life; (2) the studies of the blood-making tissues (marrow, spleen, and lymph glands); (3) the data of clinical blood examination and the methods by which they are obtained.

Without attempting to summarize the whole subject of blood formation, a few of the main facts may be indicated. The blood-making system, marrow, spleen, and lymph glands, attains only gradually the differentiation seen in adult life. In fetal life, the distinction between leukocyte-producing and erythrocyte-producing tissues is much less sharp, and throughout the whole system both red and white cells are produced. Further, in the embryo the liver shares with the organs just mentioned the function of blood production. In the adult, however, specialization has become an accomplished fact. Red cells are produced exclusively, or almost exclusively, in the bone-marrow. Leukocytes are produced in the marrow, spleen, and lymph glands. A few of the lymph glands, especially the hemolymph glands, may continue their embryonic function of producing red cells, or under the stimulus of various diseases return to their embryonic function.

The source of the different varieties of leukocytes which we find in the circulating blood in adult life is now approximately agreed upon, at any rate as regards the great majority of the cells. All varieties of granular leukocytes (neutrophilic myelocytes, polynuclear neutrophiles, eosinophiles, and mast cells) are formed in the bone-marrow. Lymphocytes are formed in the lymph glands and lymphatic tissue generally. The points still in doubt are: (*a*) Does the marrow in health furnish any considerable number of lymphocytes to the circulating blood? (*b*) What is the

source of those mysterious cells closely resembling, but not identical with large lymphocytes, and usually referred to as "large mononuclear" cells? These questions will be discussed later.

In the formation of red cells in adult life, which occurs wholly or almost wholly in the bone-marrow, the earliest stages are represented by nucleated cells somewhat larger than those seen in the circulating blood, but not so large as those seen in the fetal marrow and in the marrow of the lower vertebrates. Later in the course of this development, but before it leaves the marrow, the red cell normally loses its nucleus. Whenever, therefore, nucleated red cells are found in the circulating blood, they are regarded as immature, unfinished cells, and their presence is taken to indicate an unusual activity of the red-cell-forming tissues—probably an unusual need on the part of the body for new red cells.

In the formation of granular leukocytes in the adult marrow, we find, first, mononuclear cells (neutrophilic, eosinophilic, or basophilic), which later in the course of their development, and usually before they enter the circulating blood, have developed a polymorphous nucleus. Mononuclear neutrophiles or myelocytes are thus ancestors of the polynuclear neutrophilic cells of the circulating blood. Mononuclear eosinophiles, or eosinophilic myelocytes, are the ancestors of the polynuclear eosinophiles of the circulating blood. The mast-cell nucleus, as seen in the circulating blood, is so vague and difficult to make out that it is impossible to say just what change it has undergone since it left the marrow.

Whenever there is a call for large numbers of fresh *leukocytes* in the circulating blood, the marrow sends out, first, the accumulated stores of finished polynuclear cells, which are resting in the sinuses of the marrow. When these are exhausted, if new formation goes on rapidly and is not inhibited by the virulence of the attacking disease, the earlier stages of the polynuclear, granular cells begin to appear in the peripheral circulation. The process is very closely parallel to that which occurs when there is a call for large numbers of new-formed *red cells*. First, the accumulated stock on hand is sent out; then the half-formed, immature cells are discharged into the blood stream. Finally, if the demand for new cells is long continued, the process of blood formation may revert to an earlier (fetal) type, and we begin to see in the circulating blood cells which are strangers not only to the blood, but also to the normal adult marrow, and only to be found in the fetal marrow or in lower animals. On the part of the red-cell series, these embryonic cells are represented by the megaloblasts. Just what cells represent the earliest stages of leukocyte formation in the marrow is a point more or less disputed, but the weight of authority inclines to the belief that many of the cells seen in acute lymphoid leukemia represent this ancestral, undifferentiated type.

Most observers are now coming to agree that as we trace back each of the stocks just referred to, the red cell series on the one hand and the leukocyte series on the other, we approach a common ancestor, which is in all probability a round mononuclear, non-granular cell, with basophilic protoplasm. In all the more extreme disturbances of blood formation, whether they affect especially the red cells, as in the various types of anemia, or the white cells, as in the leukemias, we begin to find in the circulating blood,

and especially in the marrow, considerable numbers of cells which approach this ancestral type, and many which are difficult to assign to either the red-cell or the white-cell series. It is now generally agreed that in the leukemias the marrow, spleen, and lymph glands all begin to turn out cells much less differentiated, much nearer to the ancestral type than are discharged from those organs in health.

The formation of lymphocytes in the lymph glands, in the thymus, tonsils, and in the lymphatic tissue scattered diffusely about the alimentary canal and elsewhere, begins in groups called "germ centres," where cell division is especially active. From these the new-formed cells are extruded peripherally, and group themselves radially. From the periphery of these groups they reach the sinuses and are carried into the lymphatic stream and into the blood current. In the germ centres we have cells closely resembling the large lymphocytes of the peripheral blood. Toward the periphery of these centres we find cells of smaller size and with deeper-stained nuclei, cells, that is, which correspond accurately to the small lymphocytes of the circulating blood.

In leukemia of the myeloid type and in some conditions of infection or auto-intoxication (scarlet fever, cancer), these lymph glands may be transformed into a tissue closely resembling the marrow; all the varieties of granular leukocytes then begin to be formed, so that it may be difficult to distinguish a section of such a gland from a section of the marrow. On the other hand, in generalized tuberculosis or carcinoma of the lymph glands, the number of circulating lymphocytes may be greatly and permanently diminished (300 to 500 per cmm.—Naegeli).

All that has been said of the lymph glands holds good of the Malpighian bodies of the spleen. Normally the seat of lymphocyte production, they may be transformed in myeloid leukemia into tissue almost indistinguishable from bone-marrow; while in lymphoid leukemia ancestral (?) cells not found normally either in the marrow or in the lymph glands, cells resembling but not identical with the lymphocytes of the germ centres, begin to be formed and turned into the blood stream throughout the lymphatic system.

THE MAIN DATA OF HEMATOLOGY.

The most important facts upon which our present knowledge of diseases of the blood is built up are the following:

1. The number of red cells per cubic millimeter, as counted in the peripheral circulation.
2. The number of white cells and blood platelets, as counted under similar conditions.
3. The percentage of hemoglobin in the circulating blood.
4. The appearances of stained film specimens of the peripheral blood.
5. The appearances of smears and sections of the blood-making tissues, marrow, spleen, and glands.
6. The gross changes in those portions of the blood-making system accessible to our examination, namely, the spleen and external lymph glands.
7. The clinical manifestations relating to other organs and tissues.

The Enumeration of Blood Cells.—Briefly stated, our method of obtaining an estimate of the richness of the peripheral blood in *red corpuscles* is: (*a*) To obtain a measured quantity of capillary blood by puncture; (*b*) to dilute this with a harmless solution, which will enable us to separate and so count the red cells; (*c*) to enclose a measured quantity of the diluted blood in a chamber of measured size, on the floor of which the corpuscles are allowed to settle; (*d*) to count the number of cells in a measured area of the floor of the "counting chamber." The floor of this counting chamber is ruled off in squares of known size, and since the cells resting on it have settled out of a known bulk of fluid, which in turn corresponds to a known bulk of blood, we may compute from the number of cells thus counted what was the number in a cubic millimeter of the blood.

It is well to indicate some of the limitations of this method and some of the possible sources of error. The actual enumeration as described gives a fairly accurate idea of the number of cells in the unit of peripheral blood selected for study; but when we come to draw conclusions from the figures thus obtained, we must remember: (*a*) That these figures tell us nothing at all about the total amount of blood in the body. They represent simply the corpuscular richness of a small, although presumably representative, specimen of the whole blood. Thus it may be that when we find in a case of advanced tuberculosis a cubic millimeter of blood containing approximately the normal number of corpuscles—5,000,000 or thereabouts—the patient is nevertheless anemic, in the sense that his tissues are bloodless, and his bloodvessels more empty than the normal. In other words, all estimates of the richness of the patient's blood by means of a count of red corpuscles must be interpreted as qualitative rather than quantitative statements.

(*b*) In certain conditions, especially in those involving cyanosis, peripheral congestion, or dropsical states, the drop which we draw may very imperfectly represent the condition of the rest of the blood mass. In cyanotic and congested conditions, red cells accumulate at the periphery, and the number which we find in a cubic millimeter of blood drawn by ordinary puncture is far in excess of the average number which would be found in the blood of the larger vessels, or within the internal organs.

(*c*) A drop of blood drawn immediately after the patient has suffered a large hemorrhage shows approximately normal conditions. Within a few days, or sometimes within twelve hours, a second count would reveal a very much smaller number of red cells per cubic millimeter. This is simply because the normal amount of fluid has been taken up by the bloodvessels from the other tissues, and ultimately from the fluids ingested. By the fluid so taken up the relatively empty vessels are refilled and the blood diluted. The second estimate after this dilution has occurred makes us aware of the loss suffered by the patient; while if we had followed the estimate made immediately after the hemorrhage, we might have supposed that no loss had occurred. It should be remembered, however, that regeneration begins so promptly that even before the blood has regained its normal bulk of fluid by absorption from the tissues, the number of red cells has begin to approach normal, owing to the rapid regeneration and extrusion of new red cells in the marrow.

The enumeration of *white corpuscles* is accomplished in essentially the same way by which the red cells are counted. By making use of 0.5 per cent. of acetic acid as a diluting fluid, we render the red cells invisible, and can count the white cells without difficulty. The many factors and influences which control the number of white cells in the peripheral blood in health and disease, and the distribution of the various types of leukocytes within the total leukocyte count, will be discussed in the section on Leukocytosis and Leukopenia.

Hemoglobin Estimation.—Since hemoglobin is, so far as we know, the important functional element in the red cells, the amount in a unit of blood would be, could we accurately measure it, equivalent to the amount of functioning red-corpuscle substance. There seems no good reason to doubt that the bulk or weight of hemoglobin in a given unit of blood can be measured with reasonable accuracy by an estimate of the intensity of the color sensation produced by that quantity upon the eye. The various clinical methods are based upon this presupposition, and the color of the blood, either diluted or undiluted, is compared with a standard scale of colors arranged to correspond with the color of normal blood, with the color of blood lacking 10 per cent., 20 per cent., 30 per cent., and so on of the normal.

Color Index.—What is known as the *color index* in hematological terminology refers to a ratio between (*a*) the number of corpuscles stated in percentages and (*b*) the percentage of hemoglobin. When the red corpuscles are 100 per cent. of their normal number, and the hemoglobin is 100 per cent. of its normal color, we say that the color index is 1; but if the amount of coloring matter per cell becomes reduced one-half, while the number of cells remains normal, so that we have 100 per cent. of corpuscles with only 50 per cent. of hemoglobin, we say that the color index is 0.5. If, on the other hand, as in pernicious anemia and in some other grave types of anemia, the red corpuscles are reduced to (say) 20 per cent. of their number, while the hemoglobin reads 30 or 40 per cent., we say that the color index is high—that is, above 1. Thus, 40 per cent. of hemoglobin with 20 per cent. of corpuscles means a color index of 2. Such a color index is generally assumed to be due to an increase in the amount of hemoglobin contained in each corpuscle.

With the application by Ehrlich of aniline dyes to the staining of blood films, our first clear insight into the details of blood pathology began. The advent of the "Romanowsky" method of staining, with its host of variously named modifications,[1] has effected a renewal of activity and interest, but also an obscuring of old landmarks, comparable to what has been produced by the "higher criticism" in biblical literature.

Staining Affinities of the Red Cell in Health and Disease.—We speak of the normal red cell in the circulating blood of adults as monochromatophilic; and of the diffusely brown, purple, or blue-stained erythrocyte as *polychromatophilic*. (See Plate X, Fig. 1, M¹, M², M³.) When the basic staining occurs as a sprinkling of blue-black dots upon the corpuscle, it is often spoken of as "*stippling*" or basophilic granulation. (See Plate XI,

[1] Nocht's, Giemsa's, Ziemann's, Jenner's, Wright's, etc.

Fig. 1.) An evidence of the immaturity of the red cell is the presence of nuclei in the cells. These nuclei, like those of most of the body cells, are marked off and made visible by the fact that they have an intense affinity for basic (usually blue-staining) dyes, so that in the nucleated red cell we have, with the ordinary methods of staining, a dark-blue or greenish-blue nucleus outlined against a yellow or pinkish cell body.

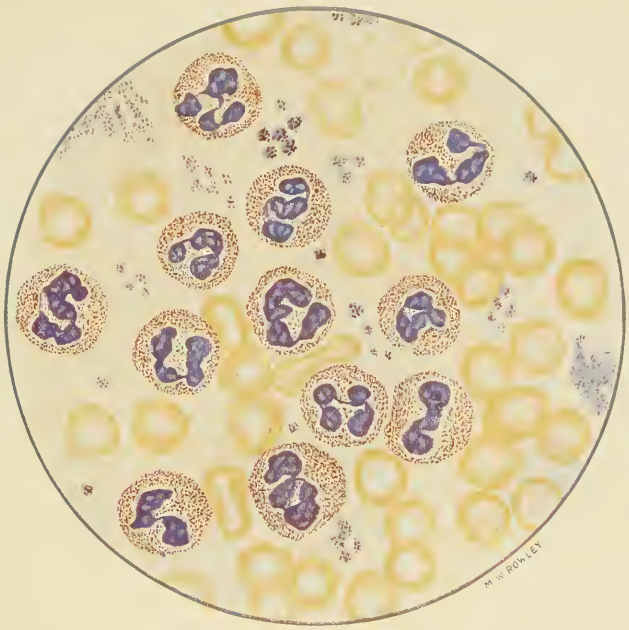
Among the nucleated red cells of human blood two main types are distinguished: (*a*) *normoblasts* and (*b*) *megaloblasts*. The megaloblast is the larger and also the younger or more primordial cell, following the well-known histological law that the ancestors are larger than their descendants. The megaloblast is a cell relatively near to the primordial mother cell, from which spring all varieties of leukocytes and red cells. This primordial cell is considerably larger than the adult red cell, has a vesicular nucleus, and a non-granular, basic, or blue-staining protoplasm. The youngest recognizable megaloblast has also a basic protoplasm, although its tint is a peculiar, dusky, cloudy blue, different from any tint seen in leukocytes. (See Plate X, Figs. 1 and 2, M¹.) In the majority of megaloblasts the hemoglobin can be recognized as fine streaks or spots of yellowish or reddish color within the blue protoplasm. The nucleus of this very young red cell takes up a very considerable proportion of the cell body, and shows a well-marked, loose-skeined structure. Later generations of megaloblasts have a protoplasm less and less basophilic, and more and more yellowish, are smaller than their ancestors, and contain a darker, smaller, more tightly-skeined ("pyknotic") nucleus. (See Plate X, Fig. 1, M⁴, and Fig. 2, M².)

Finally, at the end of this series we reach the *normoblast*, which is of the size of a normal red cell, and possesses a protoplasm which is usually, although not invariably, without basophilia. In other words, most normoblasts stain yellow or pinkish with the ordinary staining methods; but in a certain, rather small, percentage, the protoplasm contains dark-blue stained dots, or is diffusely grayish or purplish. (See Plate XI, Fig. 2, N, and Plate XII, Fig. 1, N.) The nucleus is much smaller than that of the megaloblast, and shows ordinarily very little trace of structure. It stains intensely blue or bluish-black, and is usually round. Sooner or later this nucleus disappears from the cell. As to the method of its disappearance considerable controversy has raged, one party maintaining that it is extruded from the cell, while the other party believes that it breaks up and disappears without being forced out (karyolysis). It is now generally believed that both processes occur, although probably the latter is the more frequent. At any rate, we frequently find nuclei of normoblasts separated into several pieces of various sizes, some of which stain very weakly, or are almost invisible. (See Plate X, Fig. 2, T, T, T.) Now and then a cell is seen in which only a trace of nuclear matter can be made out. On the other hand, we certainly often find a nucleus outside its cell which gives every evidence of having come from a normoblast.

Before leaving the subject of the pathology of the red cell, it may be well to mention here some morphological changes. The normal red cell is approximately round, and varies in diameter from 5 to 8 or $8\frac{1}{2}\mu$. Whenever the conditions of the production of red cells in the marrow are

PLATE IX

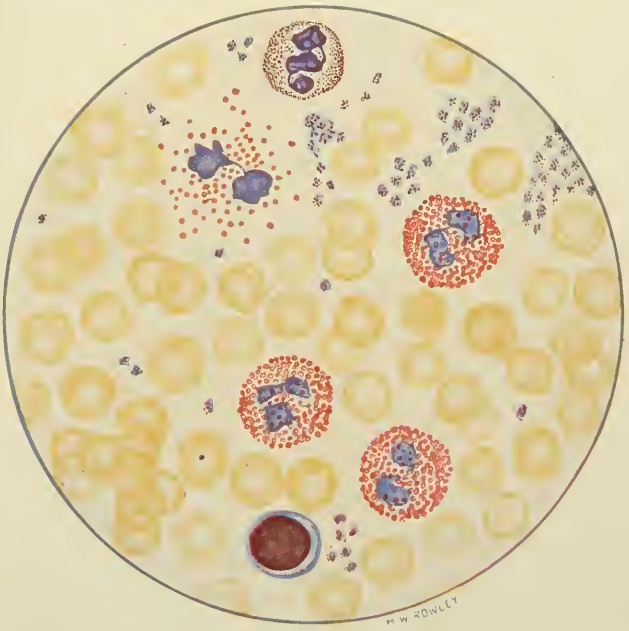
FIG. 1



Polynuclear Leukocytosis.

A reproduction of an actual field containing twelve polynuclear neutrophiles. The red cells are achromic. Blood platelets numerous.

FIG. 2



Eosinophilia (Trichiniasis).

Copy of an actual field containing three normal polynuclear eosinophiles, one broken eosinhphile, one polynuclear neutrophile, and one lymphocyte.

disturbed, as in anemias of a grave type, we begin to find in the circulating blood cells which vary much more than the normal in size and in shape—giant cells, 10 to 20μ in diameter; dwarf cells, only 2 or 3μ in diameter; and deformed cells, pear-shaped, horseshoe-shaped, oblong, etc. In some specimens of blood there is a very marked tendency toward an oval or sausage-shaped type, reminding us of the cells seen in the blood of many of the lower animals. To these morphological deviations are given the names: anisocytosis (variations in size) and poikilocytosis (deformities in shape). (See Plate X, Fig. 1.)

Staining Affinities of the Leukocytes.—To the granules which show a special affinity for one of the colors of a supposedly neutral stain was given by Ehrlich the name *neutrophilic*, which has clung to them ever since. Nevertheless, it has been shown that these granules will stain, although less distinctly, with almost any dye of the acid series. The possession of neutrophilic granules is confined in the circulating blood of normal adults practically to the polynuclear cells (see Plate IX, Fig. 1), but in the marrow we find that the mononuclear ancestors of these polynuclear cells also possess a neutrophilic granulation. Hence to these cells has been given the name *neutrophilic myelocytes*. (See Plate XII, Fig. 1, M, M, M.)

The granulations of the coarsely granular cells, recognizable in the unstained blood, were found by Ehrlich to have a special affinity for eosin and the other acid dyes, and hence were named by him *eosinophilic* cells. In all blood films stained by Ehrlich's tri-acid mixture, these granulations take a copper-brown or tawny tint, contrasting with the violet or purple shade of the neutrophilic granules. With the Romanowsky stains these granules appear a brilliant crimson. (See Plate IX, Fig. 2.)

A third variety of granules, noticed in a very small number of the leukocytes of circulating blood, takes up only basic dyes, and remains entirely unstained by Ehrlich's tri-acid mixture. With the Romanowsky stains these granules appear a dark-claret color or navy blue. (See Plate XII, Fig. 1 and Fig. 2, M A.)

In the circulating blood of normal adults there occur in every hundred leukocytes from 50 to 70 per cent. of polynuclear cells with neutrophilic granulations ("neutrophiles"); from 0.5 to 3 or 4 per cent. of polynuclear cells with eosinophilic granules (eosinophiles); and from 0.1 to 0.5 per cent. of cells with basophilic granulations. The nucleus of this last type of cell is very difficult to make out, and its shape cannot be accurately seen in most specimens. To this cell is given the name *mast cell* by most writers, although by some they are spoken of as basophiles.

Besides the three types of *granular* cells thus far described, we find in every hundred leukocytes of the normal circulating adult blood from 20 to 45 per cent. of *non-granular*, mononuclear cells, to most of which the term *lymphocyte* has been assigned by the majority of writers. Within this type at least two sub-varieties are to be distinguished. (*a*) The lymphocyte proper, a cell usually a little larger or a little smaller than a red cell, but sometimes almost twice this size. (See Plate XIII, Fig. 1.) The nucleus takes up almost the whole of the cell, stains intensely with basic dyes, especially in the smaller forms, is almost always round or oval, and shows very little structure. The protoplasm may be either faintly acido-

philic, or more often faintly basophilic. With Ehrlich's tri-acid mixture it is strictly non-granular. With the Romanowsky stain, a few bright pink granules are sometimes seen here and there around the nucleus ("azur" granules). (See Plate XIII, Fig. 2, A.) In the larger lymphocytes the nucleus stains less intensely, the protoplasm is a little more abundant, and the pink granules somewhat more numerous. Between these large lymphocytes and the forms next to be described every grade of transition occurs.

(*b*) To certain of the larger cells of the mononuclear, non-granular group, a great variety of names has been attached by different writers; thus, Ehrlich called them *large mononuclear* and *transitional* forms. Some of them certainly are identical with Türck's "stimulation cells," which of late he calls "plasma cells." (See Plate XI, Fig. 1.) Others are referred to as non-granular myelocytes (Weil), lymphogonien (Benda), myeloblasts (Naegeli), endothelial leukocytes, and by many other titles. The nucleus is relatively smaller than in the large lymphocytes, often kidney-shaped or indented, often eccentrically placed, and shows a varying amount of structure. The protoplasm is relatively abundant, sometimes decidedly basophilic, and may contain a large number of azur granules. (See Plate XIII, Fig. 2, L, L and A.) These cells make up from 1 to 10 per cent. of the leukocytes in normal blood, and are increased in a variety of pathological conditions.

Origin of the Different Types of Leukocytes.—It is generally agreed, (*a*) that in healthy adults all the granular cells, including the polymorphonuclear neutrophiles, eosinophiles, and mast cells, with their mononuclear ancestral forms, come from the bone-marrow; (*b*) that the lymphocytes are supplied to the blood largely, if not wholly, by the lymphatic tissues of the body. Concerning the origin of the group of cells last described, the large mononuclear, non-granular variety, nothing certain can be said at the present time, but it is highly probable that a considerable proportion of them have their origin in the marrow, others in the endothelium of the vessels. It is also probable that a small proportion of the lymphocytes of normal blood are formed in the marrow, but the number so formed is probably inconsiderable.

Blood Platelets.—Since the Romanowsky staining methods, which bring out the platelets sharply, have replaced so largely the methods used by Ehrlich, which left the platelets invisible, interest in these structures has been renewed. The origin, long disputed, seems now to be settled by the brilliant researches of J. H. Wright, who has presented very convincing evidence that they are pieces "pinched off" from the long processes of the marrow giant cells. They are increased in number in diseases which lead to a multiplication of giant cells (posthemorrhagic anemia, leukemia), and diminished in conditions like pernicious anemia which are associated with a marrow poor in giant cells.

Thanks to the work of J. H. Pratt and others it is now possible to obtain a fairly accurate idea of the number of these structures in the peripheral blood, and it has been definitely established (*a*) that their number varies normally between 200,000 and 700,000 per cmm., (*b*) that they are considerably increased in pneumonia, posthemorrhagic anemia and in

myeloid leukemia, and (*c*) that they are notably diminished in most cases of pernicious anemia, in many fevers including typhoid and especially in purpura hemorrhagica.

In diameter they vary from 1 to 5μ, but most of them are not far from 2μ. They are usually oval in shape and tend to gather in large clusters like a bunch of grapes. Giant forms, as large as erythrocytes, occur in the severe anemias. With the Romanowsky stains we see that they consist of a faintly blue-stained substratum, toward the centre of which a mass of magenta or dark-purple granules are clumped. No definite nucleus or structure can be made out. For practical purposes one of the most important facts about the blood plates is the danger of mistaking them for malarial parasites, an error which occurs repeatedly. When a blood plate happens to settle upon a red corpuscle it becomes surrounded (for some reason not clear) by a white halo, marking it off from the stained red corpuscle substance around it. Under these conditions it bears a superficial resemblance to a young malarial parasite, from which, however, it may be readily distinguished by the absence of any definite blue-stained ring structure and of any red-staining nucleus.

Blood-making Organs.—1. **The Bone-marrow.**—In the normal adult the marrow is only in part a hemopoietic tissue. It is composed to a considerable extent of fat, and serves presumably as one of the normal fat reservoirs of the body. The amount of this fat varies greatly in different bones, in different parts of the same bone, in different individuals, and in the same individual under varying conditions of health and disease. The fat is presented in the form of spots or islands, between which come cellular areas of erythroblastic or leukoblastic tissue. The erythroblastic areas have already been described.

In the *leukoblastic areas* we find: (*a*) Neutrophilic myelocytes (50 to 60 per cent.), with a much smaller and variable number of their maturer forms, the polynuclear neutrophiles. (*b*) A small number of eosinophilic myelocytes and polynuclear eosinophiles. (*c*) A very small number (usually less than 1 per cent.) of mononuclear cells containing basophilic granules, and their adult forms, the mast cells. (*d*) A few cells closely resembling the neutrophilic myelocytes, but almost or wholly free from granules and more or less purely basophilic in their protoplasm. (*e*) A considerable number (15 to 30 per cent.) of cells *apparently*[1] identical with the lymphocytes of the circulating blood (no definite lymphoid follicles can be made out in the vast majority of normal cases).

In addition to these varieties, all of which can be frequently recognized in the circulating blood, we have two types of cells—both of which are occasionally found in the capillaries of the internal organs, but of whose presence in the circulating blood we have as yet no clear evidence. (*f*) The macrophage or giant cell, a cell of irregular shape and varying greatly in size (between 20 and 50μ). Its nucleus is very irregular and convoluted or multiple, eccentrically placed, and stains intensely; its protoplasm is non-granular, faintly basophilic, and often occupied by a variety of inclusions, cellular and non-cellular. (*g*) The "megacaryocyte," is a smaller

[1] It is difficult in marrow preparations to distinguish lympohocytes from young red cells and from free erythrocyte nuclei.

phagocytic cell, between which and the large lymphocyte or large mononuclear cell of the normal blood there are all stages of transition. They are smaller than the giant cell, but larger than the granular myelocytes, and have a non-granular protoplasm and a round, oval, or bean-shaped nucleus, eccentrically placed and usually with a pale stain. By most writers, these cells, or at least a part of them, are thought to arise from the endothelium of the reticulum. They are by far the most actively phagocytic cells in the body. Some writers have reported the finding of megacaryocytes in the circulating blood. In marrow the last two varieties are present in scanty but varying numbers.

The islands of cellular hemopoietic tissue are most numerous in the short bones and toward the epiphyses of the long bones, and grow more and more infrequent as one passes toward the middle of the bones. The younger the individual the larger the amount of hemopoietic tissue, especially of the erythroblastic type, and the smaller the amount of fat. To this juvenile or infantile condition the marrow is prone to return when stimulated by any of a number of pathological conditions (infection, toxemia, anemia). We say then that the marrow has become *hyperplastic*, but this hyperplasia varies a great deal in type, according to the nature of the stimulus in response to which it is conceived to occur.

In typhoid fever and in variola, for example, we find hyperplastic marrow. The degree of change varies a great deal in different cases, but the hyperplasia is made up especially of mononuclear cells with basophilic protoplasm, many of them indistinguishable from the lymphocytes of the circulating blood and aggregated into definite follicles (myelocytes, 40 to 50 per cent.; lymphocytes, 30 to 50 per cent.—Longcope). In pneumonia, on the other hand, and in most other infectious diseases attended by a polynuclear leukocytosis in the circulating blood, we find marrow hyperplasia; but this time the excess of cells is made up very largely of neutrophilic myelocytes (60 to 75 per cent.—Longcope), while their mature forms, the polynuclear cells, are quite scanty (1 to 5 per cent.) probably because they are absent on duty in the peripheral blood. The more intense and long-standing the infection, the larger the proportion of myelocytes.

Thus far the conditions found in the majority of cases have been stated, but not infrequently we find that the marrow hyperplasia occurring as a result of infectious disease involves the erythroblastic, as well as the leukoblastic, tissue. The number of red cells, nucleated and non-nucleated, begins to increase, and to assist in that crowding out of the fat which is characteristic of all the marrow hyperplasias.

In the various types of anemia an erythroblastic hyperplasia or metaplasia of the marrow occurs, a change which we recognize in gross by the appearance of a bright-red color in the shaft of the long bones, a color produced by multiplication of red cells, and atrophy of the yellow fatty tissue.[1] Here the following point may be added: Anemia may give rise not merely to an erythroblastic hyperplasia or metaplasia, but also to an increase in the amount of leukoblastic tissue, that is, to a lymphoid or

[1] "Red marrow" can also be produced by simple congestion.

myeloid change. The blood may also reflect this change as in Naegeli's case of puerperal septic anemia, in which the leukocytes were 30,000, with 25 per cent. of myelocytes. Why this occurs in some cases and not in others, and why it varies so much in degree, we cannot say.

2. **The Spleen.**—For the purposes of this article, the most important facts about the spleen are as follows:

(*a*) In fetal life it is the seat of red-cell formation, to which it may return under pathological conditions in infancy and occasionally in the adult.

(*b*) It plays a part in the resistance to infectious diseases. Presumably this function is more or less closely connected with that next to be mentioned.

(*c*) It is normally the seat of hemolysis, intra- and extracellular, and of phagocytosis, so that it has been often spoken of as a "scavenger," or as a "graveyard" for defunct or superannuated red corpuscles. In disease, especially in splenic anemia and pernicious anemia, this function of hemolysis becomes exaggerated.

(*d*) It is chiefly and essentially a lymph gland, and its Malpighian bodies correspond to the follicles of lymph glands, so that after splenectomy a compensatory hyperplasia of the other lymph glands usually occurs.

(*e*) By reason of the close connection of its origin and function with those of the bone-marrow, it is very prone to undergo metaplasia, whereby it is transformed into a tissue resembling the bone-marrow either of myeloid or of lymphoid leukemia. In health it seems much like a lymph gland. In disease it often reacts more like the marrow than like the gland.

(*f*) It is often the seat of chronic inflammatory processes with varying degrees of cellular hyperplasia, in which both the follicles and the endothelium of the reticulum take part. In the more chronic forms of inflammation these changes are associated with more or less fibrous hyperplasia and metamorphosis.

3. **The Lymphatic System.**—Especially important for our purpose are: (*a*) The *peripheral lymphatic accumulations* (cervical, axillary, inguinal, epitrochlear). (*b*) The *thoracic and abdominal aggregations* (tracheal, bronchial, prevertebral, mesenteric, periuterine). (*c*) *Those surrounding the digestive tube* (tonsillar, gastric, intestinal).

We are concerned especially with the following functions of lymphatic tissue: (*a*) It is the source (at least according to most authorities) of the lymphocytes of the blood; the thoracic duct furnishes relatively few. (*b*) Like the spleen, it is concerned in the resistance to infection, in the processes of hemolysis and phagocytosis, and in the pathological hyperplasias and metaplasias. (*c*) A varying number of the prevertebral group of glands seem to be specialized to deal with red cells as well as lymphocytes. To this group the name of *hemolymph* glands has been given. In these glands we find, besides the ordinary lymph follicles, lymph sinuses and bloodvessels, a varying number of sinuses filled with red corpuscles. In these glands the destruction of red corpuscles, especially in pathological conditions such as infection and toxemia, is very considerable.

Whether or not these glands also take part under pathological conditions in red cell formation is in dispute.

Leukocytosis.—As a result probably of chemotactic influences, active especially in infectious diseases, the number of polynuclear cells in the circulating blood may become gradually or suddenly increased. This phenomenon is known as leukocytosis. This increase is made up primarily of cells summoned from the capillaries of the lung, the liver, and the sinuses of the bone-marrow, where a considerable number of these cells are normally present. If the stimulus, chemotactic or other, has continued over a considerable period, we have chronic leukocytosis, and a proliferation of neutrophilic myelocytes in the bone-marrow.

The leukocytoses have been divided roughly into *physiological* and *pathological.* Among the former the best-studied example is that occurring after violent exertion or a cold bath. As a result of these conditions, the reserve leukocytes of the lung, liver, and marrow simply shift their position and circulate in the peripheral blood. We cannot suppose that any new formation of cells occurs. There is not time. Probably of this same nature is the leukocytosis just before, during, and after parturition. In the human being there is probably no constant leukocytosis of digestion.

Pathological Leukocytoses.—(*a*) *Infectious:* As so many infectious diseases are accompanied by leukocytosis, it would be a waste of space to name them all. It is better to mention simply the exceptions, and to say that leukocytosis occurs in all infectious diseases except *typhoid fever, malaria,* most cases of *uncomplicated tuberculosis* except the meningeal form, *influenza* (most cases), *measles, mumps,* and *leprosy.*

As to the occurrence and degree of leukocytosis in the different phases of infection, the following rules hold good in the vast majority of cases:

1. If the infection is severe and the patient's resistance good, leukocytosis is early, marked, and persistent.

2. If infection and resistance are both less marked, but fairly well proportioned one to the other, leukocytosis still occurs, but comes later, is less in degree, and ceases more quickly.

3. If the infection is one of unusual virulence, as in the so-called "*fulminating*" cases of sepsis, diphtheria, or pneumonia, no leukocytosis occurs; or the increase may be altogether a percentage increase, with no gain in the total number of circulating leukocytes.

4. Occasionally, when the infection is unusually mild and the resistance unusually good, there may be little or no leukocytosis.

In septic infections, general or local, the presence and degree of leukocytosis are dependent not upon the form of the exudate, but upon the virulence of the infection. For example, in appendicitis the presence of leukocytes is no proof of pus; a gangrenous process, without pus, may produce as early and marked a leukocytosis as a purulent one, and in the so-called "catarrhal" varieties it is the mildness of the infection rather than the nature of the exudate which causes the leukocytes to remain normal or permits but a slight increase.

(*b*) *Toxic.*—In a variety of non-infectious conditions, characterized by intoxication of one or another type, leukocytosis occurs, either regularly or in a certain percentage of cases. Thus, for example, in the more cachectic

types of malignant disease we may suppose that the leukocytosis, which is sometimes present and sometimes absent, is due, when present, to the absorption of poisonous products evolved in the tumor. Other clear examples are seen in poisoning from illuminating gas, in uremia, and in the later stages of diseases involving destruction of liver tissue (*e. g.*, cirrhosis).

The *degree of increase* seen in simple leukocytosis varies in most cases between 15,000 and 30,000 cells to the cubic millimeter. Now and then one sees counts much higher than this; 50,000 or even 70,000 are not very rare, and in a number of cases the count reached above 100,000. The most marked case thus far on record, so far as known to the writer, is that of Fletcher and Sappington,[1] in which a polynuclear leukocytosis of 134,000 accompanied a case of fibrosis of the liver and spleen (autopsy). In pneumonia, malignant disease, and occasionally in sepsis very high counts are seen.

The polynuclear cells usually make up from 80 to 95 per cent. of the total increase; the presence of this percentage increase is essential to the diagnosis of leukocytosis. Some writers have maintained that a percentage increase of polynuclear cells, even without an increase in the total number of leukocytes, has the same significance and the same diagnostic importance as leukocytosis in the ordinary sense, and with this belief the writer is inclined to agree.

Lymphocytosis. — Definition. — Absolute and relative increase in the circulating lymphocytes.

Conditions of Occurrence.—(*a*) This condition, which cannot always be distinguished from the blood of lymphoid leukemia, is most marked and most constant in *pertussis*. As a rule, the counts in this disease run between 20,000 and 40,000 per cmm., being at their highest in the paroxsymal stage of the disease; far higher figures have occasionally been seen. The writer's highest count was 94,000, and much higher figures have been reported by Steven.[2]

(*b*) In some cases of sepsis, especially tonsillitis with lymphatic enlargement, we may have a lymphocytosis instead of the ordinary leukocytosis. Such cases may be for a time indistinguishable from lymphoid leukemia, but are usually recognized by their course.

(*c*) In infant's blood we have always lymphocytosis relatively to the adult. As the infant develops and its blood is approaching the adult type, any acute or chronic illness is prone to cause a return to the infantile type, with marked relative or absolute lymphocytosis.

In all the cases mentioned the increase of cells is composed wholly or chiefly of the small mononuclear varieties; but in malaria and some other diseases due to animal parasites a considerable percentage of increase in the large mononuclear forms has been noted.

Eosinophilia.—Definition.—An increase in the number of circulating eosinophiles. The most important causes are as follows:

1. *Helminthiasis.*—In a large proportion of diseases due to animal parasites eosinophilia is well marked. The best-known members of this group are trichiniasis and uncinariasis. Others are filariasis, Bilharzia

[1] *American Medicine*, August 6, 1904.
[2] *Lancet*, September 20, 1902, vol. ii.

disease, hydatid disease, and a number of diseases due to the milder varieties of intestinal parasites.

2. Acute and chronic *skin diseases*, especially those widely distributed.
3. *Bronchial asthma.*
4. *Malignant tumors* (in an uncertain but a rather small percentage of cases).
5. Myeloid leukemia (almost every case).
6. During the absorption of hemorrhagic effusions.
7. Ovarian disease (non-malignant and non-suppurative).
8. Postfebrile conditions especially after the injection of tuberculin.

In asthma and after the injection of tuberculin the eosinophilia may be interpreted as an aspect of an anaphylactic reaction.

The diagnostic value of eosinophilia is at present confined chiefly to diseases of animal parasites, and especially to the diagnosis of trichiniasis, the various intestinal parasites, and hydatid disease.

Myelocytosis.—Whenever the marrow is called upon for increased cellular production, whether the call be chiefly for leukocytes or for erythrocytes, we may find in the peripheral blood small or even considerable numbers of myelocytes. To this condition, in distinction from leukemia, the term *stimulation myelocytosis* has been applied.

It is chiefly in leukocytosis and in anemic conditions that the presence of myelocytes is noted. Thus, Naegeli has found 20 per cent. of myelocytes, with a total leukocyte count of 25,000 (absolute number of myelocytes 5000) in septicemia, and the writer many times has found smaller percentages in this same disease. Any other of the causes of leukocytosis, such as malignant disease, uremic and diabetic coma, and other toxic states, may be accompanied by myelocytosis, and Türck finds myelocytes in all acute infections, even in typhoid fever with a subnormal leukocyte count. In most cases of pernicious anemia small numbers of myelocytes, from 50 to 500 per cmm. are found. In all forms of anemia occurring in children, and especially in those accompanied by leukocytosis and splenic enlargement, myelocytes as well as other marrow elements (erythroblasts, polychromatophilic forms) are very prone to occur. In all of the conditions above mentioned it is common to find, along with the stimulation myelotosis, a small number of Türck's *stimulation forms* (plasma cells?).

Mast Cells.—Very little is known as to the causes which produce an increase of these in the peripheral blood, but personal observation suggests that the following generalization is true: Mast cells are increased in all the conditions in which eosinophiles are likely to be increased, *i. e.*, in skin diseases, in helminthiasis, and in myeloid leukemia.

Pathogenesis of the Various Types of Anemia.—Anemia in any of its forms represents the results of a greater or less degree of injury of the blood-forming and especially of the red-cell-forming tissues.

(*a*) **Secondary or Symptomatic Anemias.**—In anemias of the mildest type the red cells discharged into the blood stream are usually small, poor in hemoglobin, and vary more than normally from the standard size. A few of them contain nuclei, or exhibit staining reactions normal for the marrow and especially for the fetal marrow, but abnormal in the full-grown red cell. We may conceive of this type of anemia as representing a condition

in which the normal erythroblastic functions are strained to their utmost and are sending out cells in a more or less immature condition, while yet no radical change has taken place in the type of blood formation. In such anemias we find postmortem that the erythroblastic centres have undergone hyperplasia and have crowded out the fatty marrow, so that the color in much of the tissue in the shafts of the long bones is red instead of yellow. The factory is working overtime, and has enlarged its plant; it is beginning to do more or less poor work, and to send out goods in somewhat unfinished condition. Still, it has not yet degenerated or reverted to a more primitive style of manufacture.

(*b*) **Pernicious Anemia.**—In the type of anemia represented by the cryptogenetic pernicious anemia, by fish tapeworm anemia, and by that seen in chronic hemolysis from accidental or experimental blood poisons, the erythroblastic centres may revert to the fetal type, and we get what Ehrlich has termed a *megaloblastic degeneration.* Seen in gross, the marrow is usually bright red, as in ordinary secondary anemias, but under the microscope we find that instead of the ordinary sized red cells, with or without nuclei, we have a great number of much larger cells (megalocytes), many of them nucleated (megaloblasts). It is now generally assumed that this megaloblastic degeneration is the result of an inapt and unsatisfactory attempt at regeneration, an attempt to make up somehow the losses produced by destruction of the red cells in the peripheral circulation. A call, chemotactic in nature, as is generally assumed, summons the marrow into increased and distorted activity, and the result is a hyperplasia, or still more a metaplasia, in which the place of the erythrogenetic centres is taken by cells of the fetal type.

It should, however, be noted that the stimulus, whether chemotactic or not, does not act solely upon the red-cell-forming activities of the marrow; the hyperplasia which occurs is not wholly of erythroblastic tissue; there is also a hyperplasia of the leukoblastic portions of the marrow, so that in some cases the crowding out of the fat is brought about quite as much by an excess of leukocytes as by the megaloblastic metamorphosis. Some of the new-formed leukocytes find their way also into the blood stream, and when the number which are thus extruded into the bloodvessels is unusually large, puzzling clinical pictures may occur, and clinicians are sent fishing for new names, such as "leukanemia." But the fact which should have been more fully realized ere this new term was coined is this: The stimulus, as the result of which megaloblastic metaplasia occurs, is *not strictly specific*, does not exert its influence wholly upon the erythroblastic tissue; it is to a certain extent a stimulus to the whole blood-forming apparatus, and the whole of this apparatus may respond with hyperplasia. The results of this are seen especially in the marrow, but also to some extent in the spleen, liver, and lymph glands, where the number of marrow leukocytes may be considerably increased.

(*c*) **Aplastic Anemia.**—Sometimes there is no response to the call. The marrow is unable to make up the losses produced (we assume) by hemolysis, and, instead of an increase in the bulk of erythroblastic tissue, we find an actual atrophy; that is, we find fatty marrow from end to end of the long bones, and in the peripheral blood a decrease in the granular

leukocytes and a total absence of immature red cells and of cells of the fetal types, which indicate (in other types of anemia) that the bone-marrow is in a state of unusual, even though warped, activity.

Aplastic marrow and aplastic anemia differ, however, only in degree, not in kind, from the type found in ordinary pernicious anemia. In some cases considerable areas of active marrow remain in a part of the osseous system, especially in the ribs, where Naegeli found in one typical case islands of hyperplastic (retrograde-undifferentiated) marrow with 95 per cent. of marrow lymphocytes (myeloblasts) and numerous megaloblasts.

(*d*) **Myelophthisic Anemia.**—In all the varieties above described, anemia has seemed to be the result primarily of a destruction of the fully formed red cells, rather than of a primary failure on the part of the erythroblastic tissues. But in the type of anemia which occurs as a result usually of leukemia, sometimes of neoplasms involving the bone-marrow, we customarily assume that the erythroblastic tissue has been starved out, or pushed to the bony wall enclosing it, by the overgrowth of other cells, leukoblastic or neoplastic.

It is probable, however, that this process is only in part responsible for the anemia which we find in the terminal stages of most cases of leukemia. The accumulations of iron-bearing pigment, which we find in the liver, spleen, and lymph glands of many cases of leukemia, suggest that hemolysis may be in part responsible for the anemia which we are apt to think of as a simple pressure anemia or a crowding out of the breeding places of the young red cells.

CHAPTER XVI.

PERNICIOUS AND SECONDARY ANEMIA, CHLOROSIS, AND LEUKEMIA.

By RICHARD C. CABOT, M.D.

PERNICIOUS ANEMIA (CRYPTOGENETIC).

Definition.—A chronic and usually fatal disease of unknown origin, producing, especially in elderly men, paroxysms of intense anemia and usually degeneration of the spinal cord.

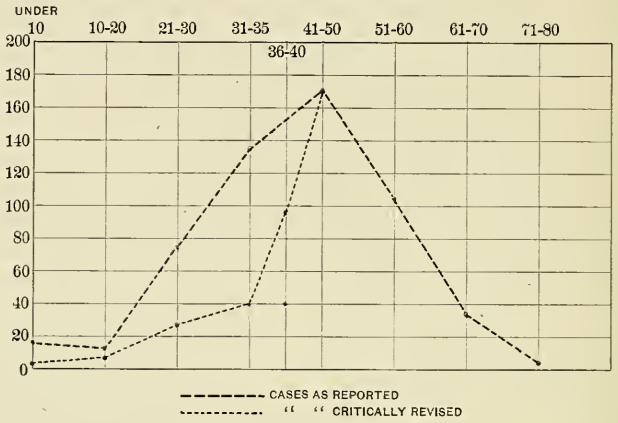
Material.—In preparing this article the writer has put together all the cases seen by him during a period of twelve years, both in hospital and private practice, 337 in all. To these are added 320 collected through the kindness of my friends in different parts of this country from their unpublished records of hospital and private cases. All the cases accessible in the literature of this subject which bore the test of a critical scrutiny have been gone over, and 543 selected. All the statements of this article are based upon the analysis of these 1200 cases, together with a consideration of the easily available literature. As a rule, the two groups of cases, which are distinguished arbitrarily as "American Cases" and "Foreign Cases," show, when analyzed, substantially the same, in some items almost identically the same, results. When the divergencies are marked, both sets of figures are given in the text.

Frequency and Conditions of Occurrence.—There seems good reason to believe that the disease is not at all uncommon, nothing like so rare, for example, as leukemia or myxœdema. At first sight one is tempted to believe that it is much commoner in certain localities than in others, but more careful study seems to show that the disease is commonest wherever it is most carefully sought; that is, in the vicinity of men who have trained themselves to recognize it. There is no reason to believe that it is any more common in New England than in other parts of this country, although at first glance the statistics might seem to suggest this. It has been suggsted repeatedly that the disease is more common in rural districts than in cities, but these figures do not, on the whole, give any support to this hypothesis. Most of the writer's patients have been residents of large towns or small cities, rather than of the more sparsely settled country districts or of larger cities. The writer twice found the disease in the same family, two sisters being attacked in one instance, and a brother and sister in another; but the disease does not appear to be hereditary in the strict sense.

Age.—In Figs. 53 and 54 are represented the facts regarding the ages of the 1200 cases on which this article is based. A glance at these tables makes it obvious that it is a disease of elderly people, its incidence being

not far different from that of cancer. The more carefully one studies the cases, whether at the bedside or in literature, the rarer does it appear to find a typical case of pernicious anemia before the thirty-fifth year. A small number of cases occur in the early months of infancy, but these cases

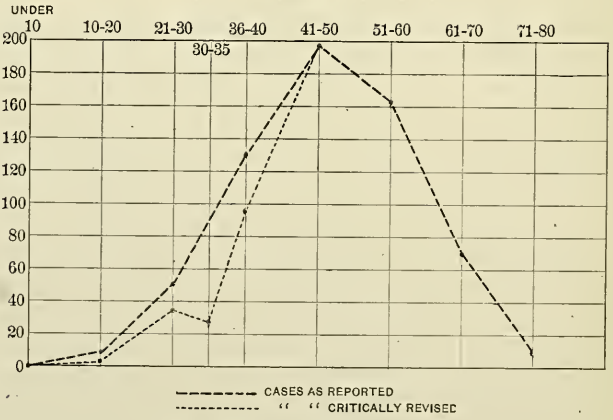
Fig 53



Age diagram of 535 foreign cases.

are rarely typical; that is, they usually present one or more considerable divergencies from the average obtained from the analysis of any large series. In the decade ending with the tenth year there are less than ten well-authenticated cases on record. This figure is slightly increased in

Fig. 54



Age diagram of 621 American cases.

the next decade, and considerably increased in the decade ending with the thirtieth year; but in these decades (tenth to thirtieth year) the number of cases depends upon two factors: (*a*) how far back in the literature of the disease we go, and (*b*) whether we include cases originating

during pregnancy or shortly after parturition. If these cases are excluded, the disease may be said to be distinctly rare under the thirty-fifth year. Even including them, more than half of all the cases collected occur between the fortieth and sixtieth years. By putting together all the cases over thirty-six years of age and all those under thirty-six, we get the following figures: Under thirty-six years, 149, and over thirty-six years, 922, from which it appears that the disease is between six and seven times as common after the thirty-fifth year as before it. This feature has not been so strikingly manifest in the studies of the disease made previous to this time, partly because among the younger cases many have been included which do not properly belong there, such as the aplastic anemias and those due to acute sepsis.

Sex.—Out of a total of 1157 cases available for study in this connection, 723 occur in males and 434 in females. In other words, the disease is almost twice as common in men as in women. The difference has been apparent in all the larger collections of statistics previously reported, but has never been so marked as in this one. The reason is probably the same as that just given, namely, that among the younger patients previous writers have included many (mostly women) that do not properly belong there. It is interesting to note that in the period before the thirty-sixth year the number of cases in men is almost the same as the number of cases in women—69 men and 75 women. A marked difference will be observed when compared with the figures taken from cases at all ages; that is, although *twice as common in men as in women after thirty-five, it is slightly commoner in women under that age.* These figures are not essentially different in the two groups of cases distinguished as "American" and "Foreign."

Race, civil condition, residence, occupation, habit of body, and time of year do not seem to have any special bearing. At one time the writer had a series of cases in the wives of physicians, but further experience has shown that this was a coincidence. Hygiene and education apparently do not make any difference in the liability to the disease.

Supposed Etiological Factors.—Some of the factors usually considered in relation to the etiology may be considered.

Pregnancy and the Puerperal State.—There are 35 cases among the 1200 of this series in which the disease began during pregnancy or shortly after parturition; the more carefully we study this group of cases, the larger becomes the number of those originating during pregnancy and the smaller the number of those which began after parturition. It usually turns out that no examination of the blood has been made before parturition, so that the onset has been gauged by that very unreliable test, the appearance, or complaints of the patient. The number of those originating postpartum is further reduced when we exclude those which are probably due to septicemia and those which may fairly be classed as posthemorrhagic. Excluding these we find that 18, or slightly more than half of this group of 35 cases, originated during pregnancy. These cases are presumably to be explained as the result of hemolysis, which in turn is in all probability a manifestation of toxemia brought about by the pregnant state and manifesting itself also in nephritis, eclampsia, and obstinate vomiting.

There seems to be considerable reason for separating this group of cases from the main body of those which go under the name of pernicious anemia; for, in the first place, they arise at an age which we have shown to be uncommon, judging from the table of statistics; practically all of them occur before the thirty-fifth year, and the great majority before the thirtieth. Then they occurred in the sex which in general is relatively less often affected. Third, their course is much more apt to be progressive and without the characteristic remissions ordinarily seen. Lastly, they are not infrequently curable, provided their cause is removed. For all these reasons it seems best to draw a distinction between this group of cases and the larger cryptogenetic group. When the cause of this larger group is found it will probably turn out to be distinctly different from that of the cases occurring during pregnacy and after parturition.

Reference may be made to a case studied by the writer in 1898, because it is typical of many which have been wrongly included in the previous statistics of pernicious anemia. The patient, twenty-two years of age, entered the Massachusetts General Hospital, March 17, 1898, for a profound anemia, which first excited alarm three days after the birth of her third child, *i. e.*, about four and a half weeks before her entrance to the hospital. Her symptoms were the ordinary ones of grave anemia and the blood showed 800,000 red cells and 22,000 white cells per cmm., with 10 per cent. of hemoglobin. She complained of nothing that would suggest any local lesions, and, except for the marked polynuclear leukocytosis, there was nothing to distinguish the blood from that of pernicious anemia. The leukocyte count rose gradually in the course of two weeks to 50,800. At autopsy, which occurred shortly after this count was made, we found a diphtheritic endometritis, with all the evidences of an acute sepsis. Without the autopsy this case would have been classed as one of the puerperal type of pernicious anemia, despite leukocytosis which is never seen in true pernicious anemia.

Syphilis.—Only 2 cases were found, 1 among the American and 1 in the Foreign series, which present the picture of typical pernicious anemia occurring during the course of an active attack of syphilis. All cases are excluded in which the evidences of syphilis had disappeared some years before the onset of anemia; also 2 cases of congenital syphilis with anemia, but not typically of the pernicious type. Some dermatologists state that cases of grave anemia complicating syphilis are much more common on the continent of Europe than in this country. However this may be, it is not very uncommon to see anemia of the ordinary type, later to be described as symptomatic or secondary, in the course of syphilis; but the writer has never seen a case in which pernicious anemia, properly so called, has occurred in this connection; it is probably safe to say that such occurrence is very rare. Aside, however, from the question of the occurrence of such cases, it seems best to exclude them from the group now under consideration, because we have a definite cause and a group of clinical manifestations wholly other than those with which we are familiar in the cryptogenetic cases.

Malaria.—There are no cases in this series in which the characteristic blood picture of pernicious anemia developed during an attack of unques-

tioned malaria. Malaria is mentioned in the history of 90 cases; but in almost all of these the infection came and disappeared years before the onset of the anemia; in none was the relation sufficiently close to suggest causation. It is true, that by several very competent Italian observers, and by James Ewing, of New York, the occurrence of typical pernicious anemia in the course of malarial infection has been noted. It is most convenient to exclude these cases from the group under consideration because of the presence of a well-recognized cause. In the vast majority of cases of malaria the anemia which develops is of the secondary type.

The Menopause.—Fifty-two cases of the 1200 occurred in close relation to the time of the menopause, but as the disease is especially prone to occur at this age in men as well as in women, and as the number of cases occurring just before the menopause is fully as great as those occurring just after it, there does not seem sufficient reason to connect the anemia with the cessation of menstruation.

Atrophy of the Gastric Tubules.—In 61 cases atrophy of the gastro-intestinal mucosa was noted in the autopsy record; but (*a*) the lesion is very possibly due to postmortem changes; (*b*) the number of cases in which no such "atrophy" was found is also considerable; and (*c*) even were this lesion a constant one, there would be no good reason for supposing that it is the cause rather than the result of the disease which we are studying.

Gastro-intestinal Sepsis.—W. Hunter has tried to show that the pathologically increased hemolysis in pernicious anemia has its site in the gastro-intestinal tract and its cause in sepsis, oral, gastric, or intestinal. Only in a minority of recorded cases, however, is there any evidence of such sepsis or of any connection between the gastro-intestinal tract and the hemolysis which occurs in the marrow, spleen, glands, liver, and kidneys.

Intestinal Parasites.—No case is included in this series in which there was evidence of the existence in the body of a parasite known to be capable of producing a severe type of anemia. It has been proved by Schaumann that a disease identical in all respects with pernicious anemia can be produced by the presence of the fish tapeworm (*Dibothrocephalus latus*) in the intestine, and especially by the disintegration of the segments of this worm. It is probable also that some of the many cases of severe anemia, attributable to hookworm disease (uncinariasis), are of the pernicious type; but it has seemed best to exclude these cases from the consideration in this section, because of their definitely established etiology.

The Relation of Bone-marrow to the Etiology.—It is generally agreed today that the changes which we find after death in the bone-marrow of cases of pernicious anemia are the result rather than the cause of the disease, and represent an effort, more or less intense and successful, to resist the disease and to make up for the corpuscles destroyed. Here it is sufficient to say that the rare cases of anemia due to a destruction or replacement of marrow by other tissues (bone, fibrous tissue, malignant disease) belong in a group different from that here discussed.

Chronic Diarrhœa.—In 7 of the cases analyzed in this article the evidences of anemia were preceded and accompanied by a long-standing diarrhœa. In 2 cases the duration was two years, in 2, three years; in 3, five years; in 1, ten years. The histories of these cases are not known in

sufficient detail to make it clear whether the diarrhœa was persistent or intermittent. It is well known that diarrhœa occurs as a symptom in the course of many cases of pernicious anemia; and we may well doubt whether in these cases it was cause rather than result. Anemias ordinarily seen as a result of chronic diarrhœa present a blood picture quite different from that of pernicious anemia.

Nervous Shock.—Several writers have discussed the question whether or not the occurrence of intense mental and emotional strain, such as we find ushering in the symptoms of several of the cases in this series, is to be considered as cause or result of the disease. On the whole, the writer is inclined to believe it to be a result, inasmuch as in the vast majority of cases no such factor exists, and inasmuch as such shocks certainly occur in innumerable instances without being followed by any anemia. There were 5 cases in this series in which such a shock had occurred.

Hemorrhage.—The type of anemia ordinarily seen after hemorrhage bears no considerable resemblance, either in its clinical picture or in its course, to pernicious anemia; but it seems possible that small hemorrhages over a long period of time might give rise to a true pernicious anemia, which seems all the more plausible in the light of the investigations of Bunting. Nevertheless, the evidence seems to point, on the whole, strongly against the belief that hemorrhage can produce pernicious anemia under any conditions. The writer has studied carefully 2 cases in which small hemorrhages, continued over several years, had resulted in intense anemia, with a pallor and general appearance not unlike that of pernicious anemia, but in both these cases the blood showed a picture absolutely different from that later to be described.

That hemorrhages occur as a symptom of pernicious anemia is well established. In some cases they are prominent very early in the history of the disease, and in such cases one may be in genuine doubt whether he is dealing with a case of pernicious anemia or symptomatic posthemorrhagic anemia. As a rule, however, the amount and frequency of the hemorrhages are not such as one would expect, considering the intensity of the anemia supposedly produced by them. Transfusion experiments show that the healthy human being will make up the loss of one or two pints of blood within a week, and in none of the cases recorded in this series have the losses amounted to anything like that quantity. Frequent nosebleeds and long-continued bleeding from hemorrhoids were present, each of them in 4 cases of this series. One woman of thirty-two years stated that she had had frequent nosebleeds all her life. A man aged twenty-seven made a similar statement. Yet, although it is impossible to speak with perfect assurance upon this point, it seems best to class these cases as secondary anemia, or else to consider that the hemorrhages were symptomatic rather than causative. In any case they are rare, and should not be grouped with the other (cryptogenetic) cases of this series.

Pathology.—The evidence furnished by the condition of the tissues at autopsy suggests strongly that a powerful poison has acted upon them, affecting especially: (*a*) The blood (hemolysis); (*b*) the spinal cord (systemic or patchy degenerations); and (*c*) the cells of the parenchymatous organs (fatty metamorphosis of the heart, liver, and kidneys).

Presumably as the result of an unsuccessful attempt to compensate for the destruction of red blood cells, there occurs a characteristic metamorphosis of the erythrogenetic tissues of the bone-marrow ("megaloblastic degeneration"), whereby its fatty portions are largely supplanted by active blood-forming tissue closely resembling the fetal type. The other striking result of hemolysis is seen in the accumulation of iron-bearing pigment, especially in the liver, the spleen, and the lymph glands. These changes, together with the intense pallor of all the organs, the bright-red color of the muscles, the brilliant yellow of the fat, the frequent evidences of serous effusion, and the patchy hemorrhages on the serous surfaces, make up in outline the morbid anatomy of pernicious anemia.

In the spinal cord, lesions have been found in 82 cases (or 84 per cent.) of those examined in this series, while in only 14 was the cord examined and found to be normal. The degenerations affect especially the cervical region of the cord, and most often the posterior columns. The roots, so far as yet examined, have shown no important changes. The systemic degenerations not infrequently extend much farther down the cord, although they are most extensive in its upper portion. In addition to this, patches of sclerosis are often found occupying the region of the lateral columns for considerable distances along the cervical and dorsal regions. It is of interest to note that similar lesions have been described in leukemia. In the brain no important changes have been found, although in a minority of cases minute hemorrhages are scattered here and there.

Fatty degeneration is most strikingly seen in the heart muscle, and especially in the papillary muscles of the organ, where the red surface is dappled with yellow spots about the size of a pinhead or slightly larger. In the liver and kidneys the fatty metamorphosis is often extreme. The liver is somewhat enlarged in the majority of cases and intensely yellow.

The *bone-marrow* shows the most interesting changes. (*a*) *Erythroblastic activity.* Examined in the shaft of the long bones, it exhibits in typical cases a bright-red color from one end of the bone to the other, while in consistency it is usually very soft. The red color does not in itself prove the existence of medullary hyperplasia. Congestion, as from the application of a tourniquet or from cardiac stasis, likewise produces "red marrow." Microscopic examination of smears or sections shows the presence of an unusually large number of megaloblasts, with an enlargement of the germinal centres of the erythrogenetic portion of the marrow, at the expense of all the other elements, excluding sometimes the leukocyte-forming centres and always the fat. This megaloblastic degeneration is contrasted with the normoblastic metamorphosis, which gives the bone-marrow its red color in cases of secondary anemia.

The researches of Bunting, who produced experimentally in animals a gradual, long-standing hemolysis by the injection of small doses of ricin, proved that a typical megaloblastic metamorphosis of the marrow can thus be produced, a metamorphosis identical with that seen in pernicious anemia. With larger doses of this or other hemolytic agents we get, as after experimental exsanguination, a red marrow, whose color is due not to megaloblasts but to normoblasts and normal red cells. Bunting suggests the interesting hypothesis that in pernicious anemia we are dealing with a

hemolytic process, produced by a poison which exerts its action over a considerable period of time; that in an attempt to repair the damage done by this poison, the peripheral layers of the germinal erythrogenetic centres are first "peeled off," as in ordinary secondary anemia. Then as the new-formed erythrocytes are rapidly discharged into the blood with the continuation of the hemolytic process and the prolonged stimulation and acceleration of the blood-forming activities, the germ centres, where the large, immature red corpuscles lie, become enlarged, overactive, and finally crowd out all the other tissues of the marrow, so that immature red cells, often nucleated, and of the large type characteristic of the erythrogenetic centres, are discharged into the blood.

If, as in cases of anemia due to the fish tapeworm, we can remove the source of blood destruction, the marrow returns to its normal condition, functions in the normal way, and the patient recovers. If, on the other hand, as in cryptogenetic anemia, the hemolytic agent cannot be found or removed, the marrow grows more and more bankrupt.

An increase in the amount of iron pigment, normally deposited in the liver and to a lesser extent in the spleen, has been especially insisted upon by William Hunter as evidence that the hemolysis, which is now generally assumed to be responsible for the disease, takes place in the gastro-intestinal tract. It has been shown, however, that when hemolytic agents are introduced through the blood stream itself, these iron deposits occur in the same way as in pernicious anemia of the ordinary type. We have no reason, therefore, to find in the hepatic iron deposits an evidence that the hemolytic process takes its origin from the gastro-intestinal tract. It seems much more likely, as is now generally assumed, that the unknown poison of pernicious anemia stimulates and pathologically exaggerates the normal phagocytic and hemolytic activities of the spleen, lymph glands, and marrow. The pigment in the phagocytic cells and stroma of these tissues usually fails to give the iron reaction. It is in the liver and kidneys that it is changed to hemosiderin, but the primary destructive agencies act in all probability in the hemopoietic organs themselves.

(*b*) *Leukoblastic Activity.*—The stimulus which leads to erythroblastic hyperplasia in the marrow is presumably not specific, but exerts an influence resulting in that multiplication of the marrow leukocytes which is now recognized as a common feature of pernicious anemia and as a point of kinship with infectious posthemolytic marrow hyperplasias and (through pseudoleukemia and the atypical leukemias) with leukemia. Indeed, the number of nucleated red cells is rarely more than a tenth as large as the number of leukocytes. Among the leukocytes the most striking increase is in the non-granular mononuclear basophilic cells. The granular myelocytes and polynuclears are also, but less strikingly, increased. A moderate amount of phagocytosis is usually evident.

(*c*) Occasionally the bony canal is enlarged and the bone thinned.

The Spleen.—In contrast with the regenerative hyperplasia of all the marrow is the evidence of destruction (hemolysis) or of atrophy usually found in the spleen. Sclerosis and macrophagic activity are the principal features. Spleens weighing only 50 to 500 grams are not uncommonly found. The organ is tough, brownish-red, and, as a rule, remarkably poor

in cells, especially in red corpuscles. Lymphocytes and large phagocytic cells make up the majority of cells discoverable amid the hyperplastic stroma network. Pigment, intracellular and extracellular, is abundant and stains the fibrous bands so that sometimes it can be seen with the naked eye. The more chronic the case the more sclerosis and the fewer cells. Occasionally the spleen is enlarged.

The *lymph glands* and especially the hemolymph glands show, as Warthin pointed out, lesions similar in kind but less in degree when compared with those described in the spleen.

Liver.—Besides fatty metamorphosis we find in the liver cells (especially around their nuclei) an abundance of iron pigment. Aubertin[1] surmises that it has been brought there from the spleen in the phagocytic cells which are so much more abundant than red cells in the hepatic capillaries.

Coexistence of Pernicious Anemia and Other Diseases.—Now and then in an autopsy on a patient killed by cardiac disease, cerebral hemorrhage, or other affections, we find in the stomach a small nodule of malignant disease. No one supposes that in such a case the death is due to the neoplasm, or that it produced the cardiac or cerebral lesions. But if a similar nodule is found at autopsy in a case of pernicious anemia, someone is apt to suggest that the patient's death was really due to cancer with secondary anemia, and that the clinical diagnosis of pernicious anemia was wrong. Now it is a well-known fact that in a small minority of the cases of gastric cancer a profound anemia does complicate the course of the disease, but in the writer's experience and in that of most competent observers the anemia has been distinctly different from the pernicious type. When, on the other hand, the anemia has been of the pernicious type, the cancerous nodule has been so small and so harmlessly situated that there has been no good reason to suppose that it played any appreciable part in the patient's death.

The same reasoning applies to the coincidence of pernicious anemia with varying degrees of senile atrophy of the kidney. Since pernicious anemia often occurs in a person over sixty years of age, it is obvious that a very considerable degree of senile atrophy must now and then be found postmortem, and since the renal condition known as senile atrophy differs only in degree from chronic interstitial nephritis, it is likely that in some of the cases the condition will be called nephritis and the anemia pronounced "secondary." Nevertheless, there is no good reason to believe that pernicious anemia is ever the result of nephritis.

Is Pernicious Anemia Best Called a Disease of the Blood?—So prominent are the manifestations and results of anemia in most cases of the disease that we are apt to assume that it is only the blood that is diseased. But the following facts suggest that the poison which decimates the erythrocytes exerts its effect on other organs simultaneously: (1) In some cases the spinal cord shows evidence of disease earlier and more markedly than the blood. (2) The fatty metamorphosis of the heart, liver, and kidneys is not to be explained as a result of the anemia. It is

[1] *Les Réactions Sanguines dans les Anæmies Graves*, Paris, 1905.

much more likely that the anemia, the spinal lesions, and the fatty changes are coördinate manifestations of the same unknown poison. (3) The general symptoms, weakness, dyspnœa, etc., do not always get better as the blood improves nor worse as the blood deteriorates. In other words, they are not due solely to the anemia.

Symptoms.—The onset of the disease is notoriously insidious. In only 28 out of this series of 1200 cases was there anything suggesting an acute beginning of symptoms. The great majority of patients cannot state even within six months how long they have been ill, and with many there is a vague history of gradually increasing disability, extending back for years previous to the onset of more definite symptoms. The symptom first complained of in the majority of cases is *general weakness*. This was the only symptom complained of at the onset of 12 of the 643 American cases. In 160 other cases this weakness was accompanied or preceded by one or another of the following gastro-intestinal symptoms: nausea or vomiting in 52 cases, diarrhœa in 48 cases, loss of appetite in 25 cases, indigestion in 35 cases, and sore mouth in 6 cases.

Next to the gastro-intestinal tract it is the *nervous system* which is most often the seat of complaints accompanying the early weakness. Thus in 49 cases of this series, headache, vertigo, blurred vision, or fainting were present at the onset. In 39 other cases a numbness, tingling, or other abnormal sensations in the hands and feet were noticed by the patient before any other symptoms occurred. In 20 patients mental symptoms, such as somnolence, nervous irritability, lack of energy or power of concentration, showed themselves earliest. In one very intelligent patient, who passed through five attacks of the disease, these mental disturbances distinctly preceded all other symptoms, including bodily weakness. In 2 cases loss of power in the legs was the earliest symptom of the anemia developing later than the signs referable to the spinal cord.

Besides the two modes of onset alluded to, namely, those with gastro-intestinal symptoms and those with symptoms referable to the nervous system, a smaller group is characterized by circulatory disturbances, especially dyspnœa (25 cases) and œdema (14 cases). Palpitation was also an early symptom in 8 cases. Twenty-nine patients noticed a simultaneous loss of appetite and weight earlier than any other symptom. In addition to the groups of cases already noted, there are a few unusual modes of onset to which reference may be made here. Thus, fever without any assignable cause was the first abnormality noticed in 3 cases, while in 3 others chills were among the earliest manifestations. Jaundice was the first fact called to the attention of 5 patients in this series, while in 6 hemorrhage from the nose and mouth preceded other symptoms.

Special attention should be drawn to the fact that a considerable proportion of all the patients suffering from pernicious anemia do not look very sick, nor consider themselves very ill, when they first come under observation. Of course, there are great variations, but one of the reasons why the disease is so often unrecognized is our unwillingness to attach so ominous a name to a disease which causes so little discomfort in its early stages. Thus one patient, a drygoods salesman, for months worked four-

teen hours a day in the basement of an ill-ventilated store, and at a high pitch of nervous tension, while suffering from pernicious anemia, with a count of red corpuscles considerably below 2,000,000 per cmm. It has long been this patient's habit to enjoy a swim of half a mile or so each morning before breakfast, and he continued this habit for months after the disease was advanced to the point indicated by the blood count mentioned. He usually walked to and from his work, a distance of three miles each way, at this period; and his muscles were like iron. Of course, this is an extreme case, but instances are not rare in which the patient showed a degree of muscular and mental power altogether astonishing when compared with the impoverishment of the blood.

Color.—Every patient with pernicious anemia exhibits sooner or later a striking change of color. In the early stages this change may be very slight, especially when the color index remains high. In other cases the patient first presents himself with the classical, waxy, yellow tinge well developed throughout his cutaneous surfaces. The intensity of the yellow varies very much in different cases. In 12 cases of this series it was so intense that the term "jaundice" was applied by competent observers. In many other cases the yellowish tinge of the skin and conjunctiva is sufficient to make us hesitate a good deal before deciding whether to pronounce it jaundice or not. In another large group of cases the color of the skin does not differ appreciably from that seen in other types of anemia, but the relatively good preservation of the subcutaneous fat layer gives the patient a different and peculiar appearance, although intense whitish pallor is, in fact, the only color change.

Another discoloration of the skin seen in 38 cases of this series, and frequently referred to in literature, is the brownish tint resembling sunburn, and usually attributable to the use of arsenic over a long period. Associated with this, 8 cases in our series show vitiligo or leukoderma distributed in patches here and there over the body.

In dealing with the symptoms of the established disease, after the onset is past, it seems convenient to divide them into two groups:

I. The symptoms common to all types of anemia.

II. The symptoms more or less peculiar to pernicious anemia.

Symptoms Found in Pernicious Anemia and Other Anemias.—(1) Muscular weakness; (2) dyspnœa; (3) palpitation; (4) headache; (5) vertigo; (6) tinnitus; (7) anorexia; (8) œdema.

(1) *Muscular weakness* is present in practically every case as soon as the disease is well established; it was complained of by 1101 out of 1139 cases of this series. (2) *Dyspnœa* was present in 800 out of 915 cases. (3) *Palpitation* occurred in almost every case. (4) *Headache* was present in 398 out of 697 cases. (5) *Vertigo* was present in 271 out of 455 cases, or approximately 60 per cent. (6) *Tinnitus* occurred in the great majority. (8) *Œdema*, usually affecting the legs, was seen in 330 out of 572 cases (or 57 per cent.).

Symptoms More or Less Peculiar to Pernicious Anemia.—*Gastro-intestinal crises*, or paroxysms of pain in the stomach, with or without diarrhœa, were present in 341 out of 563 (or 60 per cent.) of the American cases, and in 677 out of 953 (or 71 per cent.) of the whole series, the symp-

tom being somewhat more common in the foreign than in the American cases. Very important is the fact that periods of perfectly good digestion occurred repeatedly in almost every case, and usually covered more than half the total duration of the illness. When the gastro-intestinal symptoms supervene, it is usually impossible to trace any cause for them; they are generally resistant to any form of treatment, and seem to run a self-limited course, leaving the patient much exhausted. Yet, curiously enough, they are often followed by a marked improvement in all symptoms.

Diarrhœa, steady or paroxysmal, occurred in 464 out of 897 cases (or practically in 50 per cent.), while in 316 cases (or 35 per cent.) there was constipation, and in 166 (or 15 per cent.) constipation and diarrhœa alternated.

Of special interest is the occurrece of one or another type of *sore mouth*, a symptom to which William Hunter has drawn special notice, since he believes it to be connected with the etiology of the disease. Careful note was made regarding the condition of the mouth in only 372 cases of this series. Of these, 159 showed some form of sore mouth, usually a diffuse hyperesthesia, affecting especially the tongue, and associated with a bright-red, beefy appearance. Several of the patients complained of this symptom very early in the course, possibly before any other discomfort was felt. In other cases there was ulceration, more or less severe, or herpetic lesions. It will be noted that the percentage of cases with sore mouth (42) is not far from that of the cases with diarrhœa (40 per cent. in the American cases; 65 per cent. in the foreign).

Symptoms Referable to Disease of the Spinal Cord.—We may divide the cases into three groups: (*a*) Those in which the symptoms of anemia precede and overshadow those referable to the spinal cord. (*b*) Those in which the spinal symptoms appear earlier, or give rise to more discomfort, than those produced by the anemia. (*c*) Those in which symptoms of this type are trifling or absent, despite the presence, postmortem, of well-marked lesions in the spinal cord.

In the majority of all cases of pernicious anemia we have no symptoms that could possibly be referred to spinal disease except numbness, tingling, or other abnormal sensations in the hands and feet. These are present in almost every case, even in some which have shown postmortem no changes in the spinal cord. Hence, we cannot properly attribute them to any cord disease. Aside from these paresthesias, the cases with important spinal symptoms may be divided roughly into two groups: (*a*) those in which we have a spastic gait, with increased reflexes, and a greater or less degree of paralysis, and (*b*) those in which the symptoms are strongly suggestive of tabes dorsalis, the reflexes being diminished and ataxia prominent. In this series there were 46 cases of the spastic type and 75 of the tabetic type, while in 2 cases the symptoms in the earlier part of the disease were of the spastic and later of the tabetic type. In most of the spastic cases, anesthesia, with incontinence of urine and feces, gradually developed. There is a small group (6 cases), in which the symptoms were like those of a diffuse myelitis, with complete paralysis of the four extremities and relaxation of the sphincters.

In addition to these relatively advanced and complete pictures of spinal disease, there are many cases in this series which show a variety of what might be called "fragments" of the complete clinical picture. For example, *ataxia*, or unsteady gait, with or without Romberg's symptom, was present in 25 cases. *Lightning pains* were complained of by two patients, who had no other obvious signs of tabes. *Girdle sensation* was mentioned by five and *loss of sexual power* by four. The following *paralyses* are also mentioned: of the arm in 2 cases, 1 transient; the face and one arm in 1 case; foot-drop in 1 case; hemiplegia in 3 cases, 1 of which was transient and 1 accompanied by symptoms of apoplexy; general convulsions in 5 cases; twitching of the hands occurred in 1 case.

Sensory symptoms, with the exception of the paresthesia above referred to, are rare. In one patient there was intense pain in all the extremities, and at times in the trunk, but this is very exceptional. Two patients showed pains in the arms and legs, *only on exertion*, the symptoms reminding one of intermittent claudication. Painful cramps were present in two patients, without exertion. Hyperesthesia, usually of the extremities, was mentioned in 9 cases. In one patient the diagnosis of hemorrhage into the cord was made by a prominent neurologist.

There is no doubt that the number of cases showing one or more of the lesions above described is much larger than the statistics suggest. In the reports sent in by certain of the physicians who were good enough to allow the use of their cases there is almost no mention of spinal symptoms, while other physicians, especially those who have written upon this phase of the subject, find spinal symptoms in a large proportion of all cases, a finding, which, judging by the postmortem results, probably represents the truth.

Mental Symptoms.—In the great majority of patients there are no striking psychical abnormalities. The patient becomes gradually dull and drowsy as the anemia progresses, and for a number of days before death may be altogether comatose; but in a small group—102 of the 647 American cases—there are interesting disturbances of mental balance. As few of the cases in the series were seen by alienists, the classification and diagnosis of mental symptoms are far from accurate.

Delirium is mentioned in 44 cases, definite delusions in 14 cases, and hallucinations in 8 cases. A "morbid psychosis," not further analyzed, was noted in 13 cases. Dementia was definitely diagnosed in 9 cases, 2 of which had been treated for a number of years in asylums for the insane, 1 for twenty-nine years. Depression of the melancholic type was mentioned in 3 cases, and mania in 3 cases. Hysteria was noted in 1 case studied by Weir Mitchell. It is interesting that in 3 of the markedly insane cases the mental symptoms preceded the manifestations of anemia by a number of months. The antemortem coma mentioned above was prolonged in one case to two weeks. One patient complained of morning blindness, which passed off as the day wore on. Presumably these mental symptoms are to be explained as a part of the general toxemia, rather than as a result of the minute hemorrhages sometimes found in the brain.

Hemorrhages.—The prevalent impression that there is a strong tendency to hemorrhage in pernicious anemia is true, provided we include the small

retinal hemorrhages and the small petechiæ seen so frequently postmortem on the serous surfaces. But if we search for evidence of hemorrhages of considerable size from mucous membranes (nose, gums, stomach, rectum) or under the skin, we find them in only a small minority of the cases. In only 153 (or 23 per cent.) of the 647 American cases was there any such hemorrhage. Of the foreign cases, 29 per cent. showed gross hemorrhage. (In aplastic anemia bleeding is more common.) In the American cases the hemorrhages were distributed as follows: nose in 53, rectum in 54, mouth and gums in 21, skin in 15, uterus in 13, bowels in 10, stomach in 10, lungs in 2, ear in 2, and urinary passages in 2. In only 15 of these cases did the hemorrhage amount to more than a few ounces of blood. Those from the nose, the ear, the uterus, and the rectum were the most extensive. In one case the loss of a pint of blood from the left ear was the first notable symptom.

Retinal Hemorrhages.—In the American series 238 cases were examined, and 84 (or 31 per cent.) showed hemorrhage. In the foreign series 326 cases were examined, and 236 (or 72 per cent.) showed hemorrhage. The discrepancy here is very marked and is probably due to the fact that in the foreign cases retinal examinations were made more frequently, especially in the latter months of the patient's life. In most of the American cases only a single examination (made when the patient first entered the hospital) is recorded. Probably the foreign figure, 72 per cent. is much, nearer the truth. The American figures prove only that retinal hemorrhages are less common in the early stages.

Physical Examination.—(*a*) **Color and Nutrition.**—On the whole, the most striking feature in the physical examination is the scantiness of abnormal physical signs, exclusive of the changes in the blood. The yellowish color seen in the great majority of cases which have progressed beyond the earliest stages has been described. While this engages our attention, we are apt also to note another important fact—namely, the relatively good preservation of the fat layer, which makes the cases contrast sharply with other cachectic cases. The preservation of subcutaneous fat is usually relative, rather than absolute. That is, the patient has lost surprisingly little when we consider the duration and severity of the illness. Many of the patients, as will be seen, have actually lost weight, yet the loss is often trifling, and, as we examine the patient, we find still a considerable amount of subcutaneous fat. In 728 (or 61 per cent.) out of 1182 cases in which this point was specially noted, there was no considerable loss of weight; while in 454 (or 39 per cent.) there was loss of weight. These figures are evidently very accurate, as the percentage in the American is almost exactly the same as that in the foreign group.

(*b*) **The Circulatory System.**—1. *The Heart.*—In a small number of cases, 85 (or 18 per cent.) of the 468 in our series, there was demonstrable enlargement of the heart, presumably owing to dilatation. It is remarkable, on the whole, that this dilatation occurs no oftener than it does. In a few cases it is extreme, especially on the right side of the heart, so that marked tricuspid insufficiency occurs, but in the majority we find nothing of the kind. The rate and rhythm of the heart are usually not markedly

abnormal. The blood pressure is very low; indeed, there are few diseases in which low records have been so often found. Readings of 60 and 80 mm. of mercury for the systolic pressure with the Riva-Rocci instrument, and a 14 cm. cuff, are not unusual. *Murmurs* were present in 857 (or 76 per cent.) out of 1123 cases in which they were carefully listened for. It is surprising to find that there are as many as 266 cases (or 24 per cent.) in which no murmurs at all were heard. One is inclined to think that there are many errors in this observation, for among the writer's 342 cases there was not one without a murmur. Among the murmurs recorded in 812 cases, 258 were audible with about equal intensity all over the precordia, 206 were best heard at the apex, 86 at the base of the heart, 48 over the pulmonary artery, and 12 at the aortic area. In 25 cases the murmur was equally loud at the apex and in the pulmonary region. In 12 cases it was equally loud at the apex and in the aortic area. In 142 cases we have a record simply of a systolic murmur whose point of maximum intensity is not specified. Besides these murmurs, which are those often classed as "hemic," or "accidental," there were 14 murmurs *presystolic in time* and heard best at the apex. In 2 of these autopsy showed no lesion of the valves; in the others there were none of the other confirmatory signs of mitral stenosis, and we may surmise that the murmur was functional in type, but there is no certainty on this point. *Diastolic murmurs* were present in 9 cases, 4 of which were shown at autopsy to be free from valvular lesions. These diastolic murmurs were probably due to that unusual elasticity of the cardiovascular system which is so often present in grave anemias of any type.

2. *Unusual Vascular Pulsations.*—In 327 (or 42 per cent.) out of 763 cases an unusual pulsation of some of the arteries was noticed. This was especially often seen in the carotids, which are spoken of as "flapping," or violently beating. In one case reported by Edwards,[1] a pulsation in the upper left portion of the chest and abdomen was so violent that aneurism was confidently diagnosed during life, although nothing of the kind was revealed at autopsy. In many other cases a "collapsing pulse" is mentioned. There is no reason to believe that these unusually noticeable pulsations of the larger arteries are in any way characteristic of pernicious anemia. Ashford and others have called attention to similar pulsations in cases of anemia of various grades dependent upon hookworm disease, and they are repeatedly seen in intense secondary anemia. Since autopsy usually shows an unusual thinness and elasticity of the larger arteries, we may reasonably suppose that this is the explanation of these unusual pulsations. They may be also explainable in part by diminution in the total quantity of blood, a fact pointed out some years ago by Haldane and Smith, and since confirmed by other observers. It is presumably for this reason that those who make the mistake of trying to obtain blood by puncture of a finger-tip are often unsuccessful in this disease. Blood can always be obtained with ease from the lobe of the ear.

3. *Œdema.*—Among 1019 cases 642 (or 64 per cent.) showed manifest œdema. The percentage is somewhat higher in the foreign cases than

[1] *Transactions of the Association of American Physicians*, 1902, p. 182.

in the American group, but the discrepancy is not marked. The œdema usually affects the legs, occasionally also the hands. Serous effusions were present in 108 (or 30 per cent.) of 357 cases in which this point was carefully studied. The chest is most frequently affected, but occasionally there is marked ascites as well. How far this œdema and these serous effusions are explainable as the result of simple mechanical weakness of the heart, and how far due to some of the other and more mysterious causes of œdema, we are in no position to judge.

(*c*) **The Respiratory System.**—Beyond dyspnœa and the evidence of serous effusions in one or both chests there is little or nothing worthy of note on the part of the respiratory system. A cough is rarely present, and, except on exertion, the patient experiences no difficulty in breathing. Curiously enough, the oxygen exchange is actually increased in some cases, and is rarely below the normal.

(*d*) **Gastro-intestinal System.**—The conditions of occurrence of the ordinary symptoms referable to the digestive tract have been noted. Physical and chemical examination of the stomach reveals the following: There is rarely any dilatation of the stomach, and when it is present it is slight or moderate in degree. While it is true that in the paroxysmal attacks of bad digestion, with diarrhœa and vomiting, there may be well-marked motor insufficiency of the stomach, this disappears as the attack passes off, and is not characteristic. Chemical examination of the stomach shows, as has been pointed out by Stockton and others, that hydrochloric acid is usually absent or greatly diminished, while the digestive ferments, less often tested for, have also been found, as a rule, to be absent. Among the records of 79 cases seen by the writer in which the gastric juice was tested, only in one of this number was hydrochloric acid found in any considerable quantity. In other words, we may say it is practically always absent. This seems to hold good as well of the stages in which digestion is good as of those in which it is bad. This achylia has usually been explained as the result of an atrophy of the gastric mucosa, which autopsy showed to be present in 61 cases of this series. A small group of cases is on record which demonstrate that we may have complete achylia without atrophy of the gastric glands, and it is probable that this atrophy when present is usually a postmortem phenomenon. The *x*-ray examination gives a picture often wrongly interpreted as due to gastric cancer. The outlines about the pylorus are obscured and stasis may be present.

Liver.—Demonstrable enlargement of the liver was present in 364 out of 1023 cases (or 35 per cent.) of this series (33 per cent. American and 38 per cent. foreign). There are usually no other symptoms referable to the liver, unless we include as such the slight or moderate degree of jaundice seen in some cases. Gall-stone attacks have been associated in the course of 3 of the writer's cases, but this is probably a coincidence.

Spleen.—Enlargement was demonstrated in 290 out of 1045 cases (or 27 per cent.) of this series (22 per cent. American and 34 per cent. foreign). The enlargment was usually slight, the edge of the organ being just palpable below the ribs, but in perhaps 1 per cent. of the cases it was considerably enlarged, reaching nearly or quite to the level of the navel.

Glandular enlargement, slight or moderate, was recorded in 123 out of 691 cases (or 17 per cent.). There is no reason to attribute to it any special significance in relation to this disease.

Several writers have referred to the presence of tenderness over the long bones in this disease, as well as in leukemia, with the implied suggestion that it had some special significance. Personal experience, however, coincides with that of many others in showing that such tenderness is present only when there is either œdema of the part or a general hyperesthesia. There is no reason for connecting it in any way with the changes in the bone or bone-marrow. Tenderness at the junction of the manubrium with the rest of the sternum has been recently pointed out in connection with a few cases of pernicious anemia, as well as of leukemia, but in the former disease it has probably little significance.

Fever.—Considerable elevation of temperature was present in 475 out of 568 cases (or 79 per cent.). This fever is sometimes continued over one or more weeks at a time, so that the diagnosis of typhoid fever has been seriously considered in two of the patients seen by the writer. As a rule, however, the fever is lower and more irregular than that of any of the common infectious diseases. Its presence indicates a relatively severe type of disease, or a severe stage. During the remissions fever is absent.

Urine.—The twenty-four-hour quantity is usually about normal, sometimes diminished, but rarely markedly so. The color, contrary to the impression given by William Hunter, is usually very pale, and the pigments diminished. Albumin was present in 236 out of 506 (or 46 per cent.) of the American cases, and albumin with casts in 119 (or 24 per cent.) of the cases. The amount of albumin was usually very small, but in 11 cases it was large. Casts were present, without albumin, in 3 cases. The casts were usually of the hyaline or finely granular types.

Blood.—I. *Gross Physical Characteristics.*—(*a*) Haldane and Smith were the first to demonstrate that the total quantity of blood in the body in pernicious anemia was markedly diminished.

(*b*) A drop of blood, as it emerges from a puncture, is often surprisingly well colored, owing to the relatively high percentage of hemoglobin. One often says to himself, on looking at such a drop, "This cannot be pernicious anemia," and yet finds, on further examination that the case is a typical one. Sometimes the corpuscles and plasma divide from each other in such a way as to give the drop a streaked appearance.

(*c*) Talquist called attention some years ago to the fact that when a drop of blood in a case of pernicious anemia is soaked into a piece of bibulous paper, the red spot produced by the blood becomes surrounded by a pale ring, slightly but distinctly darker than the surrounding dry paper. While wet, this ring appears like colorless moisture, but as the blood stain dries, the ring persists, and is seen to have a slight grayish tint of its own. This ring, while not absolutely characteristic of pernicious anemia, is rarely seen in any other disease.

(*d*) The abnormal fluidity of the blood makes itself apparent as soon as a drop is drawn by puncture.

(*e*) The clot usually retracts in a normal way. It is in aplastic cases that retraction is deficient.

II. *Quantitative Changes.*—Regarding the rate at which the count of red corpuscles descends from the normal to the figure at which we find it when the patient first presents himself, we can form some conjecture by studying the rate of its descent in the relapse after one of the periods of improvement, which so often occur. Judging from these data, we should suppose that it takes the blood from six months to a year to degenerate, in the majority of cases, to the point where we find it when the patient first presents himself for advice. This point was below 2,000,000 red corpuscles to the cubic centimeter in 599 (or 84 per cent.) of the 715 American cases in which there is a record of the blood, and in 393 (or 89 per cent.) out of 438 foreign cases. Obviously, then, it is the rule for a patient to get along without feeling sick enough to consult a physician throughout all the earlier stages, and until the blood has reached what we should naturally consider an alarmingly low point. It is notorious that we rarely see these cases until they are "full blown," as it were; we rarely have the opportunity to watch the beginning of the disease. At the same time the latter is not unknown, for in 20 cases of the American series the blood count was between 3,000,000 and 3,500,000 when the patients first consulted a physician. In the foreign series this figure is much lower, presumably because a larger proportion of hospital cases was included.

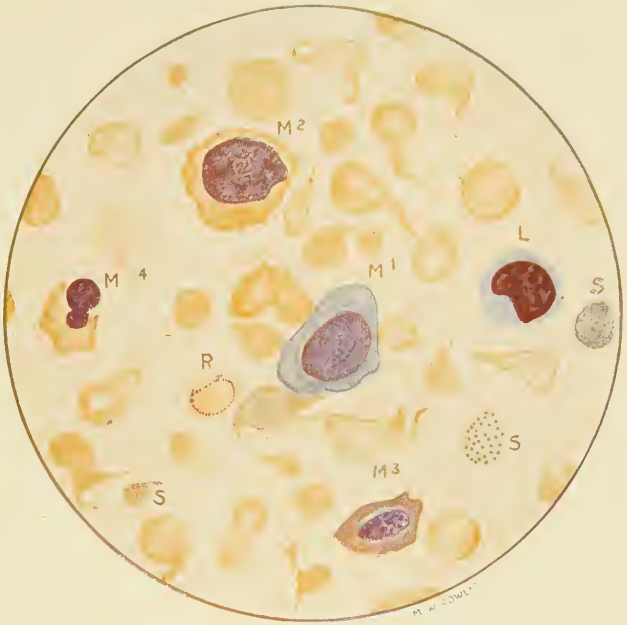
Most remarkable is the fact that in 150 of 716 American cases the patient got along without a physician until his blood had actually reached a point below 1,000,000 corpuscles to the cubic centimeter. Indeed, some of these patients do not seem nearly as sick as some of those in whom the count is above 2,000,000 or even 2,500,000, for at the onset, as in the later stages of the disease, there is no close parallelism between the blood count and the intensity of the symptoms.

The movement of the curve representing the number of red corpuscles during the remissions which are so characteristic of the disease is of considerable interest. It is very rare to find the red count rising actually to or above the normal, even when the patient is feeling perfectly well and seems to be so in every other respect. Thus in only 4 out of 192 cases of the American series, in which this point was carefully studied, did the red count rise above 5,000,000 to the cubic centimeter, and in only 30 (or 15 per cent.) did it rise above 4,000,000. From 2,500,000 to 4,000,000 usually represents the highest point reached, and 141 of our 192 cases fall within these figures. If we compare the figures with those seen in other types of anemia met with in temperate climates it is obvious that pernicious anemia differs in degree, as well as in kind, from all but a very few of the cases met in practice. There is no other disease which *often* reduces the number of red corpuscles below 2,000,000, no other disease, that is, of temperate climates.

Our interest in seeing how low the count of corpuscles may fall during life is no longer so great, since we have realized that some patients die with comparatively slight reduction in the number of red corpuscles, while others are able to do hard work despite a much greater impoverishment of their blood. Quincke's case still holds the record with 143,000 per cubic millimeter. It is of some interest to know that this patient afterward improved greatly, and went through one of the typical remis-

PLATE X

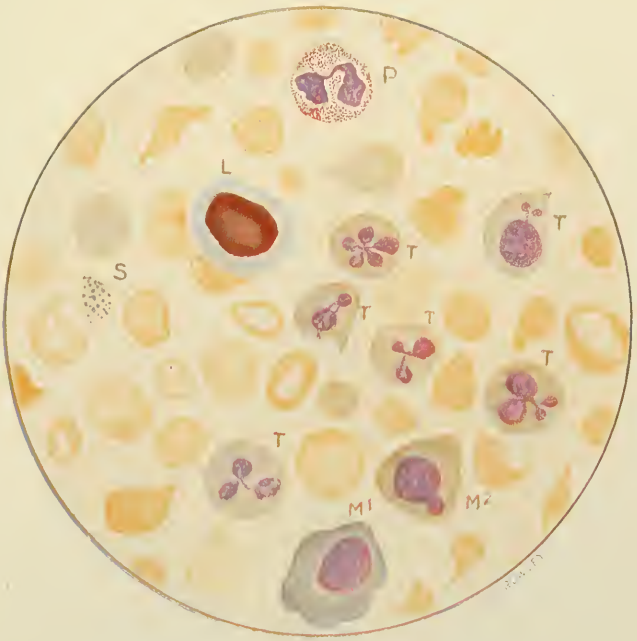
FIG. 1



Pernicious Anæmia.

The field shows marked anisocytosis and poikilocytosis: M^1, young megaloblast (early generation); M^2 M^3 M^4, later generations of the megaloblast series; *S S S*, "stippled" red cells; *R*, ring body (nuclear remnant ?); *L*, lymphocyte.

FIG. 2



Pernicious Anæmia. (Actual Field.)

Field showing less poikilocytosis than Fig. 1: M^1, young megaloblast; M^2, megaloblast of later generation; *T T T*, etc., transitional erythroblasts, not typical either of the megaloblastic or of the normoblastic series; *S*, "stippled" erythrocyte; *P*, polymorphonuclear neutrophile; *L*, large lymphocyte.

sions of the disease before she died. Two other cases with counts below 200,000 have since been reported.

Qualitative Changes in the Red Corpuscles.—The percentage of hemoglobin, although greatly reduced, is usually relatively high; high, that is, when compared with the percentage of red corpuscles. "The color index," is very constantly and characteristically high in pernicious anemia. A color index of 1 or more was present in 681 out of 920 cases of this series (or 74 per cent.). Even when the color index is below 1, it is usually so little below that figure as to contrast strongly with most other types of anemia. This high color index is due no doubt to the large percentage of macrocytes or oversized red corpuscles, containing an unusually large amount of hemoglobin.

As the disease progresses, the color index becomes higher and higher, while in the remissions it goes much lower. Thus, at the time when the count of red corpuscles was at its lowest, which may be taken as corresponding roughly with the worst stages of the disease, the color index was high (that is 1 or higher) in 713 out of 808 cases (or 88 per cent.). On the other hand, when the red count rises toward normal, and the patient begins to feel better, the color index is apt to fall; that is, the patient gains more rapidly in the number than in the quality of his red corpuscles, many of the newly formed cells being abnormally poor in hemoglobin. In the American series, out of 395 cases examined with reference to this point during a remission, that is, when the red count was at its highest, 203 cases (or 51 per cent.) show a color index below 1.

Examination of the Stained Blood Film.—Although a great deal may be learned by an examination of the fresh blood, much more can be learned by making use of stained blood film. (See Plate X, Figs. 1 and 2.)

(*a*) *Poikilocytosis*, or variation in the shape of the red corpuscles, is usually extreme. There is no other disease in which marked poikilocytosis is so often seen. Other types of anemia occasionally show the same thing, and occasionally one sees cases of undoubted pernicious anemia in which the cells are very slightly deformed.

(*b*) *Size of Red Cells.*—Careful measurements of a large number of cells usually show that the average diameter is increased. Although it is true that, on the whole, oversized cells predominate, there are also a great many dwarf cells, some of which are so small that they may easily escape notice, especially in the enumeration of red corpuscles with the Thoma-Zeiss instrument. *Excess of oversized* cells, and presumably an increase in average diameter, was demonstrable in 408 (or 92 per cent.) of our 444 cases in which special attention was given to this point. *It is one of the most constant and characteristic blood changes in pernicious anemia.*

(*c*) *Abnormalities in Staining Reaction.*—Diffuse polychromatophilia was present in 284 (or 92 per cent.) of 308 cases in which special attention was paid to this point. Spots of dark-blue or blackish discoloration upon the yellow or red stained ground of the red corpuscle ("stippling") were present in 115 of 191 cases. Neither of these changes is characteristic of pernicious anemia, but, with the exception of lead poisoning, there is no other disease in which they are so frequently seen.

(*d*) *Nucleated Red Corpuscles.*—*Megaloblasts* were found in 671 (or 94 per cent.) of 713 cases, and absent in 42 cases. In only 21 of these 42 cases was more than one blood examination made. In other words, we may say that there were but 21 (or 3 per cent.) of the 713 cases in which it was difficult or impossible to find megaloblasts. Since the number of nucleated red cells in the peripheral circulation often varies sharply from day to day, at any one examination they may easily be overlooked. Of the 21 cases without megaloblasts, 18 are probably or certainly to be classed as anemia of the *aplastic type.*

Normoblasts were present in all but 34 of 713 cases. The number of megaloblasts exceeded the number of normoblasts in 256 (or 60 per cent.) of 422 American cases. Of the foreign cases, only about one-quarter showed an excess of megaloblasts. This discrepancy between the two groups of cases is very possibly explainable by a difference in the definition of what constitutes a megaloblast. In most of the American cases the *abnormally large size* of the cell containing the nucleus was taken as the characteristic mark, without any regard to the size or structure of the nucleus itself. In many of the foreign cases presumably other criteria were used.

The Leukocytes.—*Quantitative Changes.*—Subnormal counts are the rule. Thus in 304 (or 56 per cent.) of 539 American cases the number of leukocytes was below 5000 per cubic millimeter when the patient first came under observation. In the remissions the number of white corpuscles rises with the number of red cells, so that in 48 of the American cases and 34 of the foreign cases the leukocyte count was between 10,000 and 15,000 and in 203 (or 54 per cent.) out of 374 American cases it was above 5000. The rise is equally marked in the foreign cases. On the other hand, at the time when the red count is at its lowest the proportion of subnormal white counts is greater than at any other time of the disease.

The *differential count* of the white cells shows a relatively small percentage of polynuclear cells and a relatively high percentage of lymphocytes. If we work out the percentages in connection with the total number of leukocytes per cubic millimeter, we find that the essential change is *a diminution in the absolute number of polynuclear cells*, while the number of lymphocytes remains at or near the normal. Lymphocytes of the smaller forms usually predominate. The percentage of eosinophiles is usually within normal limits. Occasionally, however, it is somewhat elevated, and in 83 out of 389 cases it was above 7 per cent. at some time in the course of the case. Fluctuations in the number of these cells are rapid and frequent, and have no known significance.

Myelocytes in small numbers are very frequently found, and now and then reach 5 or even 10 per cent.; Aubertin has reported even higher percentages. Bearing in mind, however, the small total count of white corpuscles, we see that the total number of myelocytes is insignificant, compared even with what one often finds in ordinary polynuclear leukocytoses. Aubertin calls attention to the presence of large (marrow?) lymphocytes and of Türck's "stimulation forms" ("plasma cells?") in cases in which myelocytes are conspicuous. He finds these forms especially at the period preceding a remission.

Blood Plates.—The number of these is usually very low. Thus, J. H. Pratt has shown that counts of 100,000 and less are not uncommon. This is not, however, the invariable rule, as the number of plates may be normal, or even increased, at some periods of the disease.

Remissions.—(*a*) **The Frequency of their Occurrence.**—Probably in the great majority of all cases the disease is not progressive, but is interrupted by one or more remissions in which the symptoms more or less entirely disappear. In only 95 (or 14 per cent.) of the 647 American cases was the course of the disease under observation a progressive one. In just 95 other cases the patients were steadily improving during the (relatively short) period of observation. But it is not at all likely that either of these groups gives a fair representation of the course of the disease. Probably in most of the apparently progressive cases the fragment of the disease's course occurring under observation is, in fact, the descending portion of a wave, while almost all the cases which steadily improve under treatment until they pass out of the physician's observation are at the beginning of a remission and will subsequently relapse.

Periods in which the patient's symptoms and blood counts remain stationary for months (three, four, and nine months) are not uncommon. At the end of such a pause the patient may again be restored temporarily to (or nearly to) health, but, as a rule, this is not the case, and death puts an end to the suspense. Of the American cases, 140 were wholly stationary throughout the period of observation.

The number of remissions in a single case is often difficult to fix, for in the earlier of these waves of improvement relapse the patient does not feel sick enough to consult a physician. Only by the history can we form a rough estimate, and judging in this way we get the following results from the analysis of all the available cases:

Cases with one remission	296
Cases with two remissions	118
Cases with three remissions	65
Cases with four remissions	21
Cases with five remissions	24
Total	524
Cases observed for six months or more without any remission	159
Data insufficient for judgment as to remissions	517

These data are the result of inquiries and observations regarding the patient's symptoms and general condition. The curve traced by the varying blood counts during the course of the disease corresponds only roughly with the *symptom curve*. Judging by the blood counts of the American series alone, we find the following:

	Cases.
One remission in	59
Two remissions in	22
Three remissions in	8
Four remissions in	3
Course steadily downward	95
Course steadily upward	95
Course stationary	140
Died while the blood count was rising fast	5
Data insufficient	173

Sometimes the patient will improve rapidly in strength and spirits while the blood count steadily declines; occasionally the opposite occurs. Still, in the majority of cases the movements of the blood curve run fairly parallel with those of the symptom curve.

(*b*) **Duration of Remission.**—A study of 329 cases in which the length of the patient's respite from prostration was accurately recorded shows:

	Cases.
Remission lasting one to three months in	79
Remission lasting three to six months in	85
Remission lasting six to nine months in	53
Remission lasting nine to twelve months in	100
Remission lasting two to three years in	8
Remission lasting three years in	1
Remission lasting four years in	2
Remission lasting six years in	1(?)

The great length of some of these remissions, as shown in this table, has not been sufficiently emphasized by other writers. When a man has been well and hard at work for two years or more, his physician is apt to think that there is no more fear of relapse. But the facts show that at any time the same unknown poison may again attack the tissues.

A year, as will be seen from this table, is the commonest duration of these strange pauses in the activity of the disease, and in four cases studied carefully by the writer the attack of the disease was renewed each year at the same season, sometimes in the same month. One patient had five attacks in successive years; each time the attack began in the spring, usually in March. This naturally suggests the question whether any season of the year is especially dangerous or especially favorable for sufferers from this disease. The following figures, however, give no support to such an hypothesis:

	Cases.
Improvement occurred in the spring in	82
Improvement occurred in the summer in	108
Improvement occurred in the autumn in	65
Improvement occurred in the winter in	83
Total	338

Diagnosis.—When a physician is consulted by an elderly person, usually of the male sex, who complains especially of long-standing, gradually increasing weakness, with dyspnœa and marked pallor of a yellowish cast, and when on physical examination we find that the patient has lost but little flesh and presents no notable lesions in the internal organs, except the evidence of an intense anemia and the results of this upon his cardiovascular system, then we are justified in suspecting that we are dealing with a case of pernicious anemia. This is confirmed and the diagnosis made positive by finding in the blood:

1. A reduction of the number of red cells to a point usually below two million per cubic millimeter.
2. A high color index.
3. A normal or subnormal leukocyte count.

4. (In the stained specimen). A predominance of abnormally large, greatly deformed, more or less abnormally stained red corpuscles, some of which contain nuclei.

The diagnosis is still further confirmed if the course of the disease shows one or more remissions in which the symptoms and the blood changes more or less completely disappear.

Differential Diagnosis.—I. Defining the disease as one of wholly unknown cause, our first business is to exclude all varieties of anemia due to well-recognized causes. This is to be done first by a careful examination of the stools to exclude *intestinal parasites*, looking especially for the eggs of the hookworm and the fish tapeworm.

II. Next, we must exclude the commoner types of *secondary anemia*, such as those due to gastric cancer, to chronic hemorrhage (as from piles), to malaria, dysentery, and the like. So far as personal experience goes, a careful study of the blood suffices to accomplish this purpose in every case. That is to say, no case of gastric cancer, of malaria, or of any of the other diseases which we know are apt to produce an extreme anemia has been seen in which the blood was like that described above as characteristic of pernicious anemia. In the secondary anemias the color index is lower, the count of red corpuscles usually higher, the red cells smaller and paler in the centre (achromia); the nucleated red cells are less often of the megaloblastic type, and the number of normoblasts is relatively greater. In the experience of others, however, for example, in that of Ewing[1] and of Morse,[2] cases have occurred in which a blood picture, indistinguishable from that of pernicious anemia, was associated with a cause, such as malaria, cancer, or hemorrhage, which we ordinarily think of in connection with secondary anemia. In such cases our diagnosis must rest upon the evidence of these causes. Careful search must be made for a source of hemorrhage of which the patient may himself be unaware, for gastric cancer, for malarial parasites, and other possible causes of anemia.

III. As a rule, the symptoms with which pernicious anemia arises are unlike those of any other disease. There is nothing else which often produces in an elderly person a gradually increasing weakness, dyspnœa, and pallor, without pain and without any obvious cause. The only diseases seen in which occur a group of symptoms closely approaching those just described are *myxœdema* and *arteriosclerosis*. Myxœdema may come on with all the symptoms just described and in the same insidious way, but the type of anemia is wholly different, and a careful study of the patient's mental and cutaneous symptoms will usually make the diagnosis obvious, even before the blood examination has been made. In arteriosclerosis the blood is normal. The pallor is due to the condition of the peripheral bloodvessels.

IV. *Aplastic Anemia.*—In the group of cases which it seems best to separate (under this title) young females predominate, nearly two-thirds of the recorded cases having occurred in women, and before the thirty-second year, that is, at an age much younger than that at which most cases of pernicious anemia occur. The course of the disease is invariably

[1] *Diseases of the Blood*, fourth edition, p. 800.

[2] *Boston Medical and Surgical Journal*, September 18, 1900.

acute, not chronic as in ordinary pernicious anemia. Only 5 of the 24 cases in the writer's records have lasted more than three months. The course is swift and progressive to the fatal termination. Hemorrhages are far more profuse and occur in a larger number of cases than in pernicious anemia of the ordinary type. This was the fact in 16 of the 24 cases which were analyzed. The blood also shows marked divergencies, the most important of which are the low color-index, the absence of nucleated red cells, and the high percentage of lymphocytes, 80 to 90 per cent. in most cases. These characteristics, together with a fatty, inactive marrow postmortem, are sufficient to distinguish the disease.

V. Since the spinal-cord manifestations of pernicious anemia sometimes overshadow all others, it is not very uncommon to see cases which have been diagnosed first, and not very improperly, as tabes dorsalis or as lateral sclerosis. Only by the development and recognition of the characteristic anemia can this mistake be avoided.

TABLE I.—DURATION OF ALL CASES (DEAD, ALIVE, OR UNTIL LOST SIGHT OF).

	American.	Foreign.
5 months	123	139
6 to 9 months	77	81
9 to 12 "	44	43
12 to 18 "	130	84
18 to 24 "	37	31
24 to 36 "	109	65
36 to 48 "	48	49
48 to 60 "	23	30
60 to 72 months and over	56	31
Total	647	553

TABLE II.—DURATION OF CASES KNOWN AS DEAD OR LIVING.

	American.	Foreign (dead).	
5 months and under	50	85	Under 1 year, 298 (many fragmentary cases).
6 to 9 months	30	74	
9 to 12 "	25	24	
12 to 18 "	60	48	1 to 3 years, 258 cases.
18 to 24 "	19	19	
24 to 36 "	62	50	
36 to 48 "	26	32	Over 3 years, 143 cases.
48 to 60 "	13	20	
60 to 72 months and over	36	17	
Total	321	379	

Cases lost sight of, 288.

Duration and Prognosis.—The course has been described in the section on Remissions. The duration is shown in detail in Tables I and II, where it appears that the fatal cases usually last from one to three years. On the other hand, cases not infrequently run a shorter course, so that death results within a year; while in a not inconsiderable group of cases life is prolonged three years, four years, or even considerably longer. The writer has records of 37 long cases, 10 of which lasted seven years or more, 4 for eight years or more, 6 for nine years, 9 for ten years, 3 for eleven years, 2 for twelve years, and 3 between fourteen and fifteen years. This

list includes 3 *cases which the writer regards as having recovered.* These 3 cases, all in the American series, seem to the writer to have passed beyond the period when one need fear recurrence. That is to say, when a patient has been six years free from trouble, it seems safe to conclude that no recurrence will occur. This small group of cases demonstrates the *possibility* of recovery, but when we consider that there are but 3 cases in 1200 in which recovery is known to have occurred, the frightful mortality of the disease is obvious.

Treatment.—*Rest* is undoubtedly beneficial in some cases. Some patients, whose symptoms have been steadily getting worse *as long as they continue at work*, begin to improve as soon as they are put to bed, but this applies unfortunately only to the patients who have been able to persist in work, despite the increasing anemia. To the great majority of patients for whom the disease has long since rendered work impossible, a rest cure is wholly inapplicable, because they are already at rest.

It is probable that good hygiene, including an abundance of nourishing food and a life wholly in the open air, tend to prolong life. There is no evidence so far that any special diet has any influence upon the course. By the avoidance of nitrogenous foods we can diminish intestinal bacteria, but no considerable improvement can be said to result. Several considerations have led to the recommendation of measures directed to clear the intestine of its contents more thoroughly than is ordinarily done by nature. Years ago the writer noticed that after the cessation of an attack of severe, almost intractable, diarrhœa patients would rapidly improve, even though no special treatment was then given. Acting upon this suggestion, he has in several cases administered laxatives to a point sufficient to produce two or three loose dejections each day. This treatment has several times been followed by a temporary improvement, but his experience is not sufficiently extensive to distinguish *post hoc* and *propter hoc* in this matter.

Influenced by the finding of large numbers of anaërobic bacteria in the intestine, Herter advocated a daily washing out of the large bowel through a high rectal tube, combining this with a limitation of nitrogenous food. Time has not shown that this treatment is of value.

Arsenic, given in the form of Fowler's solution or in pill, is the drug upon which the vast majority of physicians still rely. Beginning with two drops of Fowler's solution given after each meal and well diluted, the dose may be gradually increased to ten or fifteen drops three times a day, and occasionally the patient will bear even larger doses for weeks and months. One patient took seventeen drops three times a day for nearly six months. Untoward effects to be watched for are nausea and other dyspeptic symptoms; diarrhœa; itching, burning, or swelling of the eyes; brownish pigmentation of the eyes, and the evidences of peripheral neuritis. When any of these toxic effects appear the drug must be stopped until they disappear, then cautiously tried again in a much smaller dose. Occasionally patients will bear the drug better in the form of arsenious acid, $\frac{1}{100}$ grain, in pill, three times a day after food. The writer has not as yet seen any reason to believe that atoxyl, sodium cacodylate, or any other new preparations of arsenic, have any advantage over the older methods of

giving the drug, nor that there is any special benefit from giving it subcutaneously.

Inhalations of oxygen, ingestion of bone-marrow, and countless other remedies have been shown to be useless. Personally, the writer finds it difficult to believe that any drug, even arsenic, has any considerable influence over the course of the disease.

Transfusion of blood from a healthy individual to a patient with pernicous anemia is sometimes followed by a period of improvement lasting a few weeks or months.

Thorium X has been recently used and like many other forms of treatment has been followed by temporary amelioration. It is a dangerous remedy and little is known of its method of action.

Splenectomy is now the fashion in Vienna (1913). This procedure is justified by the two facts: (*a*) that the destruction of red cells in the spleen is much greater in pernicious anemia than in health and (*b*) that in splenic anemia, Banti's disease and hemolytic jaundice—diseases associated with a pathological increase of the normal hemolysis—recovery or great improvement has followed splenectomy. In pernicious anemia the first reported splenectomy was in May, 1913 (Eppenger). In no case has enough time elapsed to prove that anything more than a wave of improvement has occurred. Even this has not occurred in more than half of the cases.

Aplastic Anemia.[1]—In the group of cases described under the title of Pernicious Anemia only those in which there was a considerable degree of reactive hyperplasia or metaplasia on the part of the bone-marrow were included. But there is a smaller group in which presumably the same unknown hemolytic agent is at work, but in which the marrow responds very faintly or not at all. Instead of hyperplasia or metaplasia, we have *aplasia* or actual atrophy of erythroblastic tissue in the marrow. To these cases the name of aplastic anemia has been given. It should be remembered that the distinction between aplastic and metaplastic (or pernicous) types of anemia is one of degree only. Doubtless every sort of transition between the two types exists. In the aplastic type of pernicious anemia we find the following differences or divergencies from the ordinary picture of the disease:

1. Aplastic anemia is a disease of young persons. Of the 24 collected cases, 18 occurred before the thirty-fifth year.

2. The number of cases occurring in women is much larger than in the ordinary type of pernicious anemia; 14 out of 24 cases of this series were in females.

3. The disease runs a rapid and progressive course. There are no remissions, and the patient usually dies within a few months from the beginning of the attack.

4. Hemorrhages, subcutaneous, buccal, and of other sources, are much more common than in the ordinary type of pernicious anemia. They were notable in 16 of the cases collected.

[1] A table of cases with references is given in the first edition of this work, vol. iv, pp. 638 and 639.

5. The blood shows marked deviations: (*a*) The color-index is usually low; in 19 collected cases it averaged 0.8. (*b*) Among the leukocytes, which are usually very scanty, even scantier than in the ordinary type of pernicious anemia, all the granular types (polynuclears, eosinophiles, mast cells) are markedly diminished, so that we have a marked increase in the percentage of lymphocytes. In 12 cases of the series the lymphocytes averaged 72 per cent. and counts of 90 per cent. occurred in 3 cases. The polynuclear cells make up the rest; eosinophiles and mast cells are usually absent. (*c*) Erythroblasts, both normoblasts and megaloblasts, are usually absent. Occasionally a few may be found after a long search. (*d*) There is little or no poikilocytosis, anisocytosis, polychromatophilia, or stippling in most cases. (*e*) The blood platelets are always very scanty and more constantly so than in the ordinary type of pernicious anemia.

6. *The Bone-marrow.*—Diagnosis cannot be sure without an examination of the bone-marrow, which shows that in the long bones erythroblastic tissue has quite disappeared, leaving bones filled with fat from end to end. Of course, this describes the extreme cases, and few pathologists have the energy or the opportunity to investigate all the bones of the body with such thoroughness as would be necessary to ascertain what remnants of erythroblastic tissue are here and there remaining. Ordinarily the marrow of the femur is taken as a test. If this is yellow from end to end, the case may be assigned to the aplastic type. When any cellular elements are found they are usually lymphocytes and non-nucleated red cells.

7. The spleen shows the same condition as in the usual hyperplastic type of pernicious anemia.

Myelophthisic Anemia.—In all the types of anemia hitherto described the part taken by the bone-marrow has been passive and secondary. It has manifested simply the evidences of attempts at regeneration (more or less satisfactory) as a compensation for the unusual destruction of red cells produced by an unknown cause. But there is another group of cases in which anemia is due primarily to changes in the bone-marrow, that is, to a crowding out of erythroblastic tissue: (1) By leukemic infiltration. (2) By nodules of malignant disease. (3) By fibrous or osteoid tissues.

The most common example of myelophthisic anemia is that presently to be described as occurring in the later stages of leukemia, when the leukemic infiltration of the marrow has seriously reduced the amount of erythroblastic tissue, driving it literally to the (bony) wall. Much less common, indeed distinctly rare, are the cases in which myelophthisic anemia is the result of carcinoma or osteosclerosis, which obliterates the marrow cavity of a considerable number of bones.

CHLOROSIS.

Definition.—A disease of unknown cause, occurring only in young girls, usually between the ages of fifteen and twenty-five years, and producing moderately severe anemia.

Conditions of Occurrence.—The most remarkable fact about chlorosis seems to be the very convincing evidence that it is disappearing, at any

rate in the United States. From every one of the physicians who have been so kind in contributing cases for the preparation of this article has come essentially the same statement: "We do not see chlorosis now as we used to ten years ago." The disease seems to be dying out. It has been possible to collect less than half the number of cases which were collected from the same sources for the article on pernicious anemia. Barely 500 cases of chlorosis can be collected from the same clinics which furnished more than 900 cases of pernicious anemia, and more than half of these chlorotic cases originated in or near Boston. Yet in Boston, as elsewhere, the disease seems to be steadily diminishing. In the wards of the Massachusetts General Hospital in the year 1899, and in each of those preceding it, from 20 to 35 patients with chlorosis were treated. In the year 1905 there was but one case; in 1906 but two. The course of this decline is shown in Tables IV and V. Suspecting that this falling off might be due to the fact that the patients were now treated in the dispensary instead of being referred to the wards, the dispensary records were investigated and precisely the same condition of things found there, viz., a steady diminution of the number of cases, until in the past year we have had barely a third as many as we used to have five years ago. It is difficult to explain these facts. Certainly they are not to be explained by supposing that we now call the same cases by some other name. There has been no increase, in fact an actual diminution, in the number of cases diagnosed as *secondary anemia without any demonstrable cause*, and our system of indexing is such that if anemia or chlorosis was connected with any other disease (*e. g.*, chlorosis *with* neurasthenia or "general debility"), the chlorosis would be separately indexed and catalogued.

TABLE IV.—CASES OF CHLOROSIS AND SECONDARY ANEMIA IN THE WARDS OF THE MASSACHUSETTS GENERAL HOSPITAL, 1898–1907.

Year.	Cases of chlorosis.	Cases in the Irish race.	Cases of secondary anemia.	Remarks on the cases of secondary anemia.
1898	23	11	14	
1899	35	17	34	
1900	25	13	13	
1901	14	7	13	
1902	3	1	11	
1903	4	2	18	Only 3 cases without obvious cause.
1904	4	3	24	" 3 " " " "
1905	1	0	31	" 2 " " " "
1906	2	1	14	" 2 " " " "

TABLE V.—CASES OF CHLOROSIS TREATED IN THE OUT-PATIENT DEPARTMENT OF THE MASSACHUSETTS GENERAL HOSPITAL, 1803–1907, CASE NUMBERS 1 TO 96,000.

Among	first	10,000	cases treated	were	24	cases chlorosis	and 46	secondary anemia.
"	second	"	"		20	" "	40	" "
"	third	"	"		11	" "	51	" "
"	fourth	"	"		32	" "	41	" "
"	fifth	"	"		28	" "	31	" "
"	sixth	"	"		15	" "	27	" "
"	seventh	"	"		13	" "	40	" "
"	eighth	"	"		12	" "	30	" "
"	ninth	"	"		9	" "	13	" "
"	tenth	"	"		2	" "	8	" "

Whether the change is to be explained as a result of different conditions of immigration—fewer Irish immigrants, for example—different conditions of domestic service, or better hygiene, the writer cannot say, but the fact seems fairly well established and most interesting.

Etiology.—There is no such thing as chlorosis in the male, that is to say, there are few cases of anemia occurring in boys and young men, without obvious causes. Chlorosis is a disease peculiar to women, and practically to young women. Among 497 cases collected from the records of the Boston hospitals, and with the aid of physicians in different parts of this country, all were in women, and 468 (or 94 per cent.) occurred after the fifteenth and before the thirtieth year; 3 cases occurred between the twelfth and fourteenth years, and 26 cases between the thirtieth and fortieth. Cases occurring in this later decade almost always represent relapses. The statement implies that for the anemias seen in women over forty we can usually assign some obvious cause.

It is hard to avoid the conclusion that *occupation* has some relation to the cause of chlorosis. In this series of collected cases 209 occurred in girls employed in domestic service. In these figures, the cases (14 in number) occurring in cooks are separated from the 209 occurring in other domestics, simply because it has been supposed by some writers that cooks were especially subject to the disease, a theory which these figures do not in any way support; 64 cases occurred in girls who were doing their own housework, 20 in school-girls, 12 in waitresses, and 10 in nurses. In contrast with these relatively large figures, we find that only 7 cases occurred in shop-girls and 13 in factory-girls. The other occupations show even smaller figures.

Relatively few cases occur among the well-to-do. In making this statement allowance is made for the fact that the statistics are largely drawn from hospital records, and the statement is based upon the fact that relatively few cases are seen in private practice. The writer has had but 4 in his own practice as contrasted with 127 cases of pernicious anemia seen in the same period. It is hardly credible that the occupation of the domestic predisposes to chlorosis, and it seems more likely that the occurrence of the disease is favored by the sharp change of habits and surroundings which many girls undergo at the time when they enter domestic service. While studying the cases of this series it was striking that a large proportion of them occurred in girls who had recently come to this country, and exchanged a country life for city conditions. Similar observations have been reported in Germany, where the disease seems to be frequent among girls of German parentage who have moved to the city from the country. Apparently we have had more cases in Boston during the past fifteen years than have been observed in any other city in this country. Thus the number of Boston cases (234 out of 361) is nearly two-thirds of the total number, although all the cases recorded at the Johns Hopkins Hospital in Baltimore, and also all those available from the larger clinics of Philadelphia, Chicago, Buffalo, and San Francisco are included. The large proportion of cases observed in Boston can be attributed to the fact that the number of recent immigrants who enter domestic service, exchanging at the same time a country for a city life is larger in Boston

than in any of the other cities mentioned. Among our cases a majority occurred in the Irish race, which ten years ago (when chlorosis was common) supplied the larger number of recently immigrated domestics.

Judging from the fact that chlorosis is confined to the female, and that it occurs in the period immediately after the establishment of the function of menstruation, we can hardly help suggesting that there is some immediate relation between menstruation and chlorosis, but we can go no further. We have nothing to say as to what that relation is, or whether we are right in supposing any such relation exists. The figures suggest it; that is all we can say.

A great many "causes" have been suggested by different writers, but no one of these "causes" receives the approval of any considerable number of those who have studied the disease. Thus, Virchow's hypothesis that the disease is due to a congenital hypoplasia of the heart and bloodvessels seems incompatible with the fact that the disease can be promptly cured by the administration of iron. Meinert's observation, that gastroptosis often occurs in chlorosis, led him to suppose that this condition was the cause, but in a majority of cases the stomach is not considerably displaced, and in the remainder it may reasonably be supposed that the misplacement is a result rather than a cause. We have general muscular weakness, with laxity of the ligaments and muscles; as a part of this appears gastroptosis. An ingenious French writer called attention to the fact that slight fever and slight enlargement of the spleen are often seen, and advanced the theory that chlorosis is an infectious disease, but no infective agent has been discovered.

Many writers have called attention to the occurrence of especially poor hygienic conditions, irregular and insufficient meals, poor ventilation, and overwork as possible causes, but a study of the cases of this series does not seem to warrant any such supposition. On the whole, the hygienic conditions of domestic service, where most of these cases originated, were fully as good as those of other working girls employed in the trades, in which chlorosis is relatively rare. In the occasional cases seen among the well-to-do, poor hygiene plays no considerable part.

More plausible seems the suggestion that in some, if not in the majority, of the cases of chlorosis the anemia is secondary to an unrecognized pulmonary tuberculosis. It is certainly a fact that without careful examination of the lungs we are likely to overlook some cases of incipient tuberculosis accompanied by secondary anemia. Tuberculosis may be easily overlooked, while the anemia holds our attention and is given as the diagnosis. But the course and altogether favorable termination of a great majority of cases, without any treatment such as would tend to cure pulmonary tuberculosis, militates strongly against the idea that chlorosis is essentially a consequence of pulmonary tuberculosis.

Early cases of *hyperthyroidism* (Graves' disease) are occasionally mistaken for chlorosis, and it has been supposed by some writers that chlorotic anemia was merely a result of an unrecognized hyperthyroidism. Careful study of a large series of cases, however, does not justify this supposition. Mental and emotional causes, homesickness, unsatisfied longings, and the like have been held responsible by some, but in relatively few cases

can we trace anything of the kind. It is certainly more reasonable to suppose that these psychical manifestations are the result of a preëxisting anemia. In my opinion we know nothing about the cause of chlorosis beyond the vague guesses suggested by the statistics above tabulated.

Pathology.—Very little is known as to the anatomical basis of the disease. Indeed, the number of recorded autopsies is insignificant. Grawitz states that he has examined the marrow in the tibia of two cases of chlorosis without finding anything abnormal.

The marked tendency to venous thrombosis shows itself most often in the legs, and does not usually cause any serious injury. But in the cerebral sinuses it is not infrequent, and is the commonest cause of death in this disease. These thrombi are probably of the infectious type. In a considerable proportion of the reported cases this was evidently the case, and that it was so in the rest is further suggested by the fact that we have no reason to assume any abnormal tendency to clotting in chlorotic blood. Outside the vessels it clots, as a rule, more slowly than normal.

Symptoms.—The onset was slow and gradual in 332 (or 86 per cent.) of our 387 cases, in which special attention was paid to this point, while in 55 (or 14 per cent.) the symptoms came on rather suddenly so far as the patients' observation could discover. There were 182 of the patients who had been aware that they were not well for a period of from one to three months before they consulted a physician; 108 had suffered between six months and a year; 72 between four and six months; 44 had not felt well from one to two years; 17 from one to three years; while 3 dated their illness back more than three years.

The earliest symptoms are usually dyspepsia and muscular weakness. Practically every patient in this series complained of weakness, and in 501 out of 504 cases dyspeptic symptoms were also prominent. Among the dyspeptic symptoms, nausea and vomiting occurred in 228 cases; 183 patients complained of lack of appetite, but in the majority the appetite was capricious or perverted, rather than deficient. Distress after eating was complained of by 66 and flatulency by 57. Epigastric pain, presumably connected with digestive troubles, was complained of by 86 patients; while 26 others spoke of pains "around the heart," which are probably to be attributed to dyspepsia.

The *morbid appetite* which has been so often referred to in connection with chlorosis was noted in 128 cases of this series. The commonest abnormality was a special fondness for pickles and sour things, with a loss of interest in all other kinds of food. This was the case in 22 cases, while 19 other patients mentioned a special desire for sour food alone, and 18 patients stated that sweets were the only foods they cared for. Among the more definitely abnormal desires may be mentioned a tendency to eat chalk (8 cases), slatepencils (1 case), wood (1 case), lead-pencils (2 cases). Sand, bird-seed, dried coffee, sulphur, and magnesia were also eaten. As we look over this curious collection of articles, we can hardly fail to be struck, as many previous writers have been, with the fact that alkalies are craved, a fact that is of interest in connection with the overacid condition of the stomach. Curiously enough, gastric pain and pyrosis are rarely mentioned in this series. Constipation was definitely noted in 301

cases, and was probably unnoted in a much larger number. Constipation alternating with diarrhœa occurred in 3 cases.

Turning to *circulatory symptoms*, we find that the patients almost always complain of dyspnœa (318 cases) and of palpitation (254 cases). Œdema was noticed in 231 cases, affecting the feet and ankles in 146, the feet and legs in 37, the face in 20, the region about the eyes in 14, and the hands in 9 cases. Doubtless it is the occurrence of slight degrees of œdema which gives chlorotic patients so plump a look.

On the part of the *nervous system*, headache is by far the commonest complaint. It was mentioned in 349 cases of this series; in 72 vertigo and in 70 a ringing in the ears was also noticed. The appearance of black spots before the eyes is almost invariable, although it is actually noted in only 45 of this series. Insomnia is also more common than would be gathered from the fact that it was noted in only 64 cases of the present series. Very frequently girls speak of feeling sleepy all day, although very wakeful at night.

Pain, aside from the digestive pain referred to, is not frequently complained of; 67 patients spoke of backache, 16 of pains in the chest, 8 of pains in their shoulders, and 10 of pains all over, while in 13 more, pain was referred to some particular spot other than those mentioned.

Menstrual disturbances are common. In 120 cases the menses were noted as absent, in 81 they were irregular, in 57 the amount of flow was increased, and in 19 it was unusually painful. Leucorrhœa was complained of by 47 patients. Von Noorden's analysis of 215 cases showed that 56 of the patients (26 per cent.) had never menstruated up to the time when they came for advice, while in 129 cases (60 per cent.) there was a considerable interval between the establishment of menstruation and the beginning of the disease.

Summing up the symptomatology, we find that the patients complain especially of dyspepsia, with more or less perversion of the appetite, of constipation, muscular weakness and shortness of breath (often with palpitation and œdema of the extremities), of headache, vertigo, tinnitus, insomnia, and various (neuralgic?) pains. The menses are suppressed, irregular, or overprofuse. All of these symptoms come on rather gradually in the course of from three to twelve months in most cases.

Physical Signs.—Most striking is the color and general appearance of the patient, but it takes the eye of faith to see any justification for the title of the disease (χλόρος, green). If one exercises a great deal of imagination, one may possibly see the slightest imaginable tint of olive green in the shadow beneath the chin, but that is all. To the ordinary eye, the color is a yellowish pallor in brunettes and a whitish, although extreme pallor in blondes.

More important than the precise tint of the skin is the coexistence of marked pallor with a plump and apparently well-nourished condition of the tissues, especially when this combination occurs in a young girl. It is most important to bear in mind, however, that one sees now and then a girl with an unusually fresh, bright color who turns out on examination to be decidedly anemic. There is no safety save in the habit of testing hemoglobin as a matter of routine in every patient who consults us.

In the *examination of the chest* the most noticeable point is the presence of cardiac murmurs. Out of 220 cases of this series in which cardiac murmurs were noted, there were 112 in which murmurs were heard with about equal intensity all over the precordia. In 55 cases they were best heard at the base, in 43 at the apex, while in only 35 was it especially noted that the pulmonary area was the point of maximum intensity. In 24 cases the murmur was equally intense at the apex and in the pulmonary area. In every case the murmur was systolic in time, soft and blowing in quality, and in the majority of cases it was quite intense. The *bruit de diable,* or soft, continuous humming heard by the stethoscope over the veins of the neck, was noted in 198 cases. The murmurs above described are almost never conducted beyond the precordia, and can rarely be heard in the axilla or in the back.

Cardiac enlargement is probably more common than would be inferred from the fact that it was noted in only 94 cases of this series, but we must add at the same time, that, owing to the fact that the anterior margins of the lungs are often somewhat retracted in chlorosis (lack of full, deep breathing), an unusually large area of the heart may be uncovered in a region of the second, third, and fourth left interspaces near the sternum. Pulsation often becomes visible in this area, and the hasty observer may then conclude that the heart is enlarged. The frequent occurrence of *œdema* has been noted.

The *respiratory system* shows nothing remarkable except deficient expansion of the lungs, demonstrable upon the anterior margins.

The Abdomen.—With the exception of the occasional occurrence of enlargement of the spleen and splanchnoptosis, the abdomen shows nothing abnormal. Splenic enlargement occurred in 24 cases of this series, while gastroptosis was noted in 11. Examination of the *gastric contents* frequently shows the presence of hyperchlorhydria, but this is often fugitive, and in many cases hydrochloric acid is normal or diminished. The hyperchlorhydria is of interest chiefly because it was for so many years taken for granted that anemia must lead to a deficiency of function, and so to a deficiency of gastric secretion.

The Urine.—Albumin was present in 119 cases out of 124 tested, and casts in 42 out of 80 tested. The amount of albumin was almost invariably small, the casts few and made up almost entirely of the hyaline and granular varieties.

Fever.—Fever, slight in degree, irregular in course, is the rule in chlorosis, and was noted in 361 cases of the present series. In the milder cases it rarely reaches above 100.5° F., and is present only for a few days at a time, but in some of the severer types fever may be present constantly for weeks. The fact that fever is so constant and that it is attended by the same evidence of constitutional disturbance with which we are so familiar in pulmonary tuberculosis, must put us especially on our guard against the mistake of confusing chlorosis and tuberculosis.

The Blood.—Briefly stated, the main characteristics of the blood of chlorosis consist in a slight or moderate reduction in the number of red corpuscles and a much more marked reduction in the amount of coloring matter per corpuscle, without any other striking abnormality. There are

records of blood examination in 361 cases. In 256 of these (or 70 per cent.) the number of red corpuscles was between 3,000,000 and 5,000,000 per cmm., a relatively mild grade of anemia, while in 81 cases the number of red corpuscles was normal or even slightly above normal. Counts between 2,000,000 and 3,000,000 were found in 60 cases, and between 1,500,000 and 2,000,000 in 6 cases.

In marked contrast to these figures, which show, on the whole, only a moderate impoverishment of the blood so far as the actual number of the cells is concerned, we find that the percentage of *hemoglobin is reduced in* 278 out of 342 cases (or *more than two-thirds*) *to less than half the normal* amount, and in 202 cases out of these 278 it ranged between 20 and 40 per cent. The ratio between these percentages and the percentage of red corpuscles (the color index) is shown in Table VI, which makes it evident that in three-fifths of the cases the color index fell below 0.5. In other words, the corpuscles contained on the average less than half the normal amount of coloring matter. This is the essential feature of the blood picture.

Table VI.—Blood in Chlorosis at the Time of Entering the Hospital.

Red cells.	Cases.	Leukocytes.	Cases.	Hemoglobin per cent.	Cases.	Color-index.	Cases.
1,500,000 to 2,000,000	6	2,000 to 5,000	80	10 to 20	26	0.1 to 0.3	24
2,000,000 to 2,500,000	22	5,000 to 10,000	184	21 to 30	103	0.3 to 0.5	167
2,500,000 to 3,000,000	38	10,000 to 15,000	57	31 to 40	102	0.5 to 0.8	131
3,000,000 to 3,500,000	61	15,000 to 20,000	7	41 to 50	76		
3,500,000 to 4,000,000	81			51 to 60	39		
4,000,000 to 4,500,000	65			61 to 70	6		
4,500,000 to 5,000,000	49						
5,000,000 to 6,000,000	37						
6,000,000 to 7,000,000	2						
Total	361		328		352		322

The *white cells* show very little of interest; in 264 out of 311 cases their number was normal or sub-normal; in the remaining cases, elevations above normal were moderate and of short duration. The differential count of leukocytes was normal in 35 of the 56 cases of this series in which it was made. Only 8 showed marked percentage increase of lymphocytes. The number of eosinophiles is occasionally increased, but it is not possible to correlate this with any special type or grade of disease.

The *stained specimen* is very characteristic especially when contrasted with the appearances in pernicious anemia. The average diameter of the cells is usually reduced and never increased. Their shape is usually normal; if deformities are present they are rarely considerable. Marked poikilocytosis has never been seen by the writer in chlorosis, and there are very few records of such a condition. Abnormalities of staining reaction are not often seen, but in the severest cases, we occasionally find either polychromatophilia or stippling. The latter condition I have seen but twice. Nucleated red corpuscles are rare but not invariably absent. Eight cases of the present series showed them, although in moderate numbers. In each case they were of the normoblast type.

One of the most interesting facts about the disease, first demonstrated

by Haldane and Smith, is the marked increase in the amount of blood plasma (polyplasmia), whereby the vessels are constantly overfilled and the total amount of circulatory fluid decidedly increased. What this serous plethora may have to do with the other symptoms of the disease is as yet wholly a matter of speculation, but it is certainly a most impressive fact. *Venous thrombosis* occurred in 11 cases among the 504 here analyzed. This represents approximately the same percentage (2.2 per cent.) as in v. Noorden's 230 cases (2.1 per cent.). In this series, as in his, the extremities, and especially the legs, were involved. There was no instance of thrombosis involving the *cerebral sinuses,* such as have been reported as a cause of death by several writers.

Course and Duration.—In a considerable proportion of cases the patient is attacked more than once. Thus, 78 of this series had already had previous attacks, and it is to be presumed that in many others the disease pursued the same course, although relatively few could be followed. More than half of those whom we were able to follow relapsed at least once before regaining permanent good health. How often these relapses would occur if the patient persisted in carrying out the treatment for months as well as for the first few weeks it is impossible to say.

Under treatment the disease is usually so far relieved that the patient is able to go back to work and feel nearly, if not quite, well *within six months;* indeed, within three months 186 of our cases had returned to work. In only 16 per cent. of cases were symptoms prolonged beyond a year. The rapidity of gain varies a good deal, but, as a rule, a patient will gain 5 per cent. of hemoglobin every ten days if the treatment is steadily and effectively carried out. The writer has known but 3 of the so-called "obstinate cases" which resisted treatment for months.

Differential Diagnosis.—The diseases for which chlorosis is most likely to be mistaken are neurasthenia, pulmonary tuberculosis, the anemias symptomatic of malaria, hemorrhage or other well-known causes, nephritis, and hyperthyroidism. *Neurasthenia* may be excluded by the blood examination, since there is no anemia in the vast majority of neurasthenic patients. It is, of course, possible for the two diseases to coexist. *Tuberculosis* is to be excluded by a rigorous and searching examination of the lungs, and in cases of doubt by the *x*-rays or by tuberculin. As a matter of fact, few cases of recognized incipient tuberculosis have any considerable degree of anemia. A careful examination of the urine and of the cardiovascular system should suffice to exclude nephritis. In *hyperthyroidism* the pulse is more persistently and more decidely elevated, tremor is much more marked, and either the eyes or the thyroid gland should show prominence.

Treatment.—Chlorosis is one of the four or five diseases now known to us which can be cured with a drug; despite some hypercritical skeptics, there is no longer the slightest doubt of this fact. In any case of supposed chlorosis which does not yield readily to iron administered in the proper manner and in the proper dose, we have reason for doubting the diagnosis.

By the consensus of observers in all parts of the world, it seems now settled that the time-honored combination of sulphate of iron and potassium carbonate, in the form of Blaud's pill, is the best remedy for chlorosis.

Other forms of iron may accomplish the desired result, but none so frequently, so quickly, or with so little disturbance of the body functions. The drug should be given in the form of the five-grain pill (0.3 gm.), beginning with one pill after each meal, increasing at the end of a week to two after each meal, and at the end of two weeks to three after each meal. Rarely does a patient experience disturbances of the stomach or headache with vertigo after taking iron in this form. The drug may be given in the form of *ferrum reductum*, 1½ to 3 grains (0.1 to 0.2 gm.), in pill form after each meal. For the claims advanced for the so-called "organic" preparations of iron there is no theoretical basis, and they do not work any better than the cheaper and more old-fashioned forms advised above.

While it is a fact that patients will recover fairly quickly as a result of the administration of iron without any change in their habits, and while it is also true that patients will improve without the administration of iron, provided we correct their constipation and improve their general hygiene, it was proven to the writer ten years ago, by the studies of C. W. Townsend, that the *combination of iron* administered as above *with proper hygiene*, including the treatment of constipation, results in a cure far more speedy than can be obtained either by iron alone or by hygiene alone. As a rule, constipation is best treated by the administration of cascara sagrada, 25 drops of the fluid extract at night, or 2 to 4 grains (0.13 to 0.26 gm.) of the solid extract in pill. If anorexia is present, a bitter tonic should also be given. Under this plan of treatment the vast majority recover promptly but the patient should persist in the use of iron for at least six months after complete recovery, and should return to its use whenever there are any indications of relapse.

Now and then cases occur which resist this treatment, and which improve only after they have kept in bed for a number of weeks. In some of these, recovery is hastened by the administration of arsenic in the form of Fowler's solution, beginning with two drops well diluted, after meals, and increasing until we are warned by discomfort in the eyes or the gastro-intestinal tract that we have reached the limit of toleration. It is probably true that in some of these obstinate cases recovery may be hastened by the bleeding treatment suggested a number of years ago in Germany, but so far this measure has not found favor in this country. Several weeks of rest in bed, on the other hand, is a most valuable aid in the treatment of all severe attacks.

SECONDARY (OR SYMPTOMATIC) ANEMIAS.

All cases of anemia due to a well-recognized cause are conveniently classed as secondary. A characteristic blood picture accompanies most cases, but it is not possible to make this blood picture the distinguishing mark of the disease, because (*a*) the same blood picture is seen in chlorosis, and (*b*) some types of secondary anemia (*e. g.*, those due to intestinal parasites, or to the accidental or experimental ingestion of blood poisons, such as nitrobenzol or ricin) show the blood picture of pernicious anemia.

In a general way it may be said that the great majority of secondary anemias are mild and that their blood picture is that of a relatively mild

anemia, but to this rule also there are exceptions. Secondary anemias—due to hemorrhage, cancer, hookworm disease—may be fatal, although the blood picture remains throughout essentially of the secondary type. On the other hand, some mild stages of pernicious anemia are associated not with a mild, but with a recognizably *pernicious* type of blood. Hence the *presence of a clear cause remains our only reliable criterion for the recognition of secondary anemia.* Such causes are:

1. *Hemorrhage.* Extensive bleeding is most often traumatic or operative, pulmonary, gastric (peptic ulcer, hepatic cirrhosis, splenic fibrosis, gastric cancer), uterine (owing to miscarriage, fibroid tumors, extra-uterine pregnancy, etc.), intestinal (typhoid fever, dysentery, hemorrhoids), renal (stone, nephritis, neoplasm), vascular (aneurism), subcutaneous and submucous (leukemia, purpura, scurvy).

2. *Hemolysis,* due to (*a*) infections; (*b*) neoplasms; (*c*) blood poisons (potassium chlorate, nitrobenzol, etc.); (*d*) auto-intoxication (uremia, "cholemia," pregnancy); and (*e*) intestinal parasites.

Symptoms.—Since the symptoms are essentially identical with many of those seen in the primary anemias, the reader is referred to the sections on chlorosis and on pernicious anemia for detailed descriptions. Here it is sufficient to classify the symptoms according as they are produced by functional insufficiency (irritation or weakness) of: (*a*) *The nervous system:* headache, vertigo, faintness, tinnitus, muscæ volitantes, vasomotor disturbances, psychic irritability or weakness, insomnia, fever (?). (*b*) *The gastro-intestinal system:* anorexia, dyspepsia, nausea, vomiting, constipation. (*c*) *The circulatory system:* dyspnœa, palpitation, arhythmia, œdema, serous effusions. (*d*) *The genital system:* amenorrhœa, menorrhagia, impotence.

Acute and chronic forms of secondary anemia may be distinguished. Acute anemia is due usually to (*a*) hemorrhage, (*b*) sepsis, (*c*) malaria, (*d*) blood poisons, all causing hemolysis. Any of these causes may produce death from anemia within ten days.

Acute Posthemorrhagic Anemia.—The loss of even 50 to 70 cc. of blood produces demonstrable alterations in the corpuscles, although the patient is usually free from symptoms. The *rapidity* with which blood is lost has as much to do with the severity of the symptoms as the *amount* lost, for the patient suffers not so much from the loss of blood cells as of blood *fluid.* Hence, when there is loss of a quart of blood in small quantities, with intervals of hours or days between the hemorrhages, the vessels are each time refilled by fluid absorbed from the other tissues and (ultimately) by fluid ingested to quench thirst. Such hemorrhages, although they may produce anemia, cause the patient relatively little distress, because most posthemorrhagic suffering is due to empty vessels and the resulting feebleness of the heart's action, all of which is prevented when the hemorrhages are so spaced that the system has time to make up the loss not of cells but of plasma.

The regeneration of the cellular contents of the blood is sometimes slow, sometimes astonishingly rapid, the rate depending apparently upon the regenerative powers of the system focused in the erythroblastic marrow. As the body of an animal reacting to immunizing injections comes at last

to the rapid production of very large amounts of antibodies, so the marrow, stimulated into hyperplasia and superactivity by repeated hemorrhages, acquires in many cases the power to make up the losses with wonderful rapidity. Thus in a case of cirrhosis of the liver the third gastric hemorrhage of over a quart was made up more rapidly than the first one (a pint only), because the interval of ten days elapsed between each two hemorrhages and the marrow (doubtless) was hyperplastic. So in malaria, although the number of red cells destroyed is sometimes at least 1,000,000 per cmm. by each new generation of parasites (*i. e.*, by each paroxysm), the development of anemia may be very slow because there is time in the onset of the disease for regeneration hyperplasia.

The principal factors governing the regeneration of red cells after hemorrhage are: (*a*) The amount of time allowed for the stimulation of regenerative activity in the marrow. (*b*) The general vigor of the body. In persons whose general powers of reaction are weakened by chronic diseases such as nephritis, neoplasm, scurvy, or by lack of food, as in gastric ulcer, regeneration after hemorrhage may be slow and imperfect. Some imperfection, indeed, there almost always is. The new corpuscles are seldom as good as the old, even when their number is kept up to normal.

Animals usually do not survive the loss of one-half or more of their total blood by hemorrhage. Men apparently bear hemorrhage somewhat better than most animals, but no exact limit can be stated beyond which no further bleeding can be borne. Patients whose hemoglobin has fallen as low as 11 per cent. (Hayem) have recovered. Patients who do not die at once as a result of a single huge hemorrhage sometimes react for a few days and seem on the road to recovery, then "go into a decline" and fade out in the course of a few weeks.

The Blood.—Immediately after a hemorrhage, at the time when we wish especially to estimate its amount from the resulting impoverishment of the blood, there is no appreciable change in the single drop which we draw for examination. It is only after forty-eight hours or more that by the restitution of the volume of plasma some degree of anemia becomes evident, but even then its degree does not accurately represent the amount of blood lost, for the amount and rapidity of reproduction in the bone-marrow varies enormously in different cases.

The earliest changes are usually more evident in the stained specimen than in the count. Achromia, with slight variations in the size and shape of the cells, slight abnormalities in staining reaction, and an occasional normoblast are usually the earliest abnormalities of red-cell formation expressed in the peripheral blood; but since the stimulus, as a result of which regeneration occurs, acts not specifically on the erythroblastic tissue alone, but involves the whole marrow to a certain extent, we find both in the marrow and the circulating blood an increase of leukocytes. In the marrow it is chiefly the myelocytes and large mononuclear, non-granular, basophilic cells (lymphocytes?) that are increased. In the peripheral blood it is chiefly an increase, relative or absolute, in the polynuclear neutrophiles. With this we find, in most marked cases, a small number of Türck's stimulation forms and granular myelocytes.

A low color index is present in all except the severest cases; that is, the quality of the new-formed cell is inferior to the normal, even though the marrow may have succeeded by unusual activity in keeping the total number of red cells somewhere near the normal. The total number of red cells is usually between 2,000,000 and 4,000,000, and the color index approximately 0.5. The wave of leukocytosis (polynucleosis) which accompanies the development of anemia in most cases and disappears with the disappearance of the anemia brings the number of circulating leukocytes up to a point usually between 13,000 and 18,000 per cmm.

Summarizing the blood picture of the vast majority of cases of post-hemorrhagic anemia, we find moderate oligocytosis with polynucleosis, low color index, marked achromia, polychromatophilia, poikilocytosis, anisocytosis, a few normoblasts, and a few marrow leukocytes. This description of the blood picture after moderate hemorrhage is typical of all the other types of moderate severe secondary anemia, such as are produced by infectious diseases, neoplasms, and blood poisons.

In the severest cases, after repeated hemorrhages of large amount, the blood picture is entirely different. Thus, for example, in a case of splenic anemia the patient lost 3000 cc., or approximately three quarts of blood within forty-eight hours. About two weeks later the blood showed 700,000 red cells, 1000 white cells, and 10 per cent. hemoglobin. In the stained specimen there was no achromia; on the contrary, the cells were mostly oversized and as much deformed as in the average case of pernicious anemia. There were no megaloblasts present, but with that exception the blood might have passed for that of pernicious anemia. In the regeneration, after hemorrhages of this sort, the blood gradually returns to the achromic type with low color index, described as characteristic of the milder grades of anemia.

Differential Diagnosis.—Since hemorrhage may be a symptom as well as a cause of anemia, we need to rule out pernicious anemia and leukemia, which might be confounded with simple posthemorrhagic anemia. This is usually not difficult, for in pernicious anemia extensive hemorrhage, enough to produce marked anemia, practically never occurs in the early stages; hence, in the history we should have evidences of anemia preceding the occurrence of hemorrhage. Leukemia may be easily excluded by the blood picture. In the hemorrhagic diseases, such as purpura, hemophilia, and scurvy, the anemia is essentilly of the posthemorrhagic type, and no differential diagnosis is therefore necessary.

Prognosis.—In cases of very severe hemorrhage, if efficient treatment can be secured—that is, if transfusion can be quickly and efficiently done—the prognosis should be good in every case, no matter how great the hemorrhage, provided that the patient's strength is not already exhausted by some underlying disease, such as leukemia, uremia, or cirrhosis of the liver. If transfusion cannot be done, the infusion by physiological salt solution, subcutaneously or intravenously, is the best substitute.

Treatment.—Aside from the measures just suggested for restitution of the loss of blood, nothing but careful feeding and good hygiene is necessary. The writer is not convinced that iron and arsenic hasten the process of regeneration, but if the stomach is in good condition there is no objection

to their use. The subcutaneous injection of the citrate of iron in liquid form has not in my hands succeeded in aiding the recovery of the patient.

Acute Septic Anemia.—It is not generally realized that there is any type of acute anemia except that due to hemorrhage. The primary anemias are always chronic, and the same is true of the ordinary varieties of secondary anemia. But as a result of virulent septicemia, such as is now and then seen after childbirth and in other conditions, the red cells may be reduced below 1,000,000 within a few days; thus Grawitz has reported a case in which the red cells fell to 300,000 in less than twenty-four hours. It should be said, however, that in this case there was postpartum bleeding as well. Several cases are on record in which a few days of acute sepsis have brought the red cells below 1,500,000. This point seems of importance, as it is often assumed by clinicians that an anemia of this grade could not have been produced in a few days without hemorrhage. No doubt the destruction of red cells is the result of hemolysis in these cases, an explanation which is suggested not only by the evidences of jaundice and the changes in the urine, but also by the results of experimental hemolysis. Occasionally similar acute hemolytic anemia may result from an intense malarial infection.

Blood Poisons.—As a result of the ingestion, accidental or experimental, of hemolytic agents, such as nitrobenzol, potassium chlorate, or ricin, very severe, usually fatal anemias may develop. The type of blood change depends upon the nature and dose of the poison; some of the acutely fatal anemias produced by acetanilid or by nitrobenzol have been associated with a blood picture very much like that of pernicious anemia, although usually, as an acute sepsis, a marked leukocytosis is present. The color index is often high, the red cells oversized, and megaloblasts abundant. As a rule, however, this type is more apt to be associated with a chronic poisoning, such as has been produced experimentally by ricin.

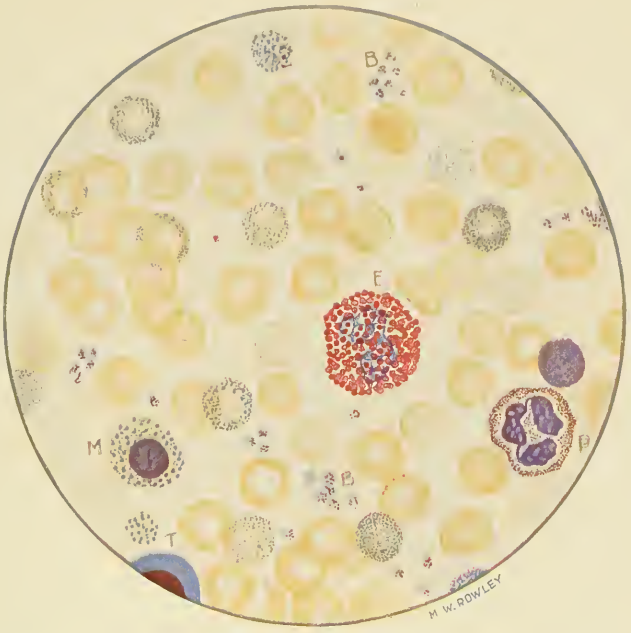
Chronic Secondary Anemia.—In cases of moderate severity, such as those associated with malaria, syphilis, chronic nephritis, hepatic cirrhosis, etc., the blood picture is usually that described in detail in the first part of the section on posthemorrhagic anemia; that is, we have the conditions often supposed to be peculiar to chlorosis, slight oligocytosis, more or less marked achromia, with low color index, slight or moderate poikilocytosis, anisocytosis, an occasional normoblast, rarely a megaloblast, and moderate degrees of abnormal staining reaction. In cases due to infectious disease or neoplasm, a polynuclear leukocytosis may also be present.

Certain peculiarities of special types of mild, chronic secondary anemia may be mentioned. In *lead poisoning* we have an extraordinary prevalence of stippled, sometimes also of nucleated red corpuscles, even in the absence of any other evidences of severe anemia. Among the nucleated red cells present, a very considerable proportion, and occasionally even a majority, may be megaloblasts. (See Plate XI, Fig. 1.) In *splenic anemia* the color index is often lower than in any disease except chlorosis. Leukopenia is often extreme, and in several cases I have noticed an extraordinarily large number of stippled erythrocytes, although the other evidences of anemia were not striking.

In the *anemias of infancy* there are certain well-marked deviations from

PLATE XI

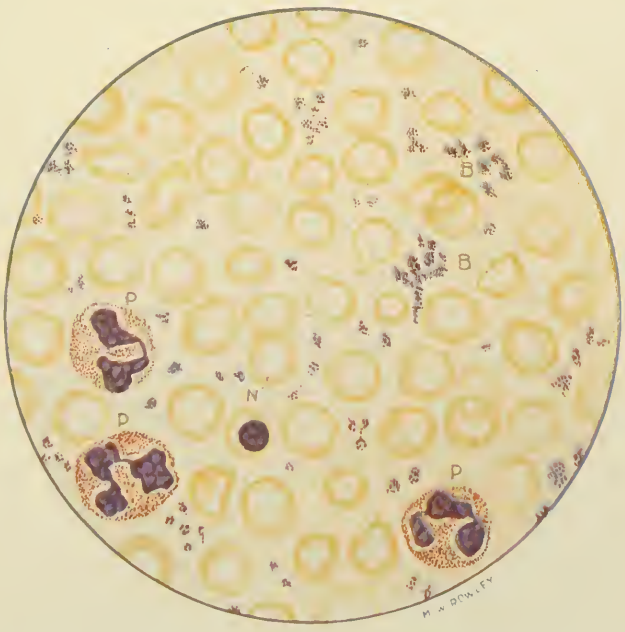
FIG. 1



Atypical Staining Reactions in Lead Poisoning. (Actual Field.)

Field shows "stippling" of various degrees and types without any marked achromia, poikilocytosis, or other sign of anæmia except *M*, stippled megaloblast; *E*, eosinophile (polynuclear); *P*, polynuclear neutrophile; *T*, Türk "stimulation form" (plasma cell ?); *B B*, blood platelets (increased in number here).

FIG. 2



Secondary Anæmia with Polynuclear Leukocytosis. (Gastric Cancer.)

The hæmoglobin was 10 per cent. (Fleischl); pallor of the centres of the red cells (achromia) is striking; *N*, normoblast; *P P P*, polynuclear neutrophiles; *B B*, blood plates.

the type familiar in the adult. Causes which produce in the adult an anemia of the mild achromic type, with small red cells and a normal leukocyte count, are apt to be accompanied in the infant by (*a*) enlargement of the spleen; (*b*) a more or less extensive leukocytosis; (*c*) a high color index and a megalocytic blood picture; (*d*) a large number of erythroblasts, among which megaloblasts are very frequent; (*e*) the presence of abnormal leukocytes (myelocytes, stimulation forms). All these facts make it much more difficult in infancy to recognize the type of blood disease and to make an accurate prognosis from the blood alone. Indeed, the attempt should never be made. Diagnosis and prognosis should depend upon the other features of the case, the nature of the cause, and the percentage of hemoglobin.

In *anemias due to intestinal parasites* the blood may be absolutely identical with that of pernicious anemia, as has been proven by Schaumann in fish tapeworm anemia, or may be rather of the achromic, small-cell type, as in most cases of hookworm disease, with which also a marked eosinophilia is also associated. In all severe parasitic anemias, however, diagnosis should rest not upon the blood findings, but upon the presence of the parasite or its eggs in the stools.

In *anemia associated with cancer*, especially that with some cases of gastric cancer, the resemblance to pernicious anemia may be very striking. Aubertin has especially insisted on this point, and has reported some very carefully studied cases in which the color index was high, the diameter of the cells large, and all the chief features of pernicious anemia accurately reproduced. The marrow, too, in his cases, was that of pernicious anemia. One cannot help being impressed by these cases of Aubertin's but they must be excessively rare. The writer's experience, both with gastric cancer and with pernicious anemia, has been very large, and no case resembling those reported by Aubertin has been seen. The large experience of the Johns Hopkins Hospital, as recorded by Osler and McCrae for cancer, and by Emerson for pernicious anemia, coincides with the writer's experience. The usual findings in the blood of gastric cancer are typical of the ordinary type of mild chronic secondary anemia, which gradually increases in intensity, but remains throughout of the achromic microcytic type.

LEUKEMIA.

Definition.—A disease characterized by enormous hyperplasia of one or more of the leukocytic elements of the hemopoietic system, elements which also flood the peripheral and especially the internal bloodvessels.

The Two Common Forms of Leukemia, Lymphoid and Myeloid.—According to the idea of leukemia that held sway from 1870 to 1900, and was supported especially by Ehrlich, the disease has two forms: (*a*) The splenic myelogenous. (*b*) The lymphatic. The first was supposed to be characterized by hyperplasia of all the marrow elements and of the spleen, the second by hyperplasia of the lymphatic glands; in both forms the new-formed cells overflow or break into the blood in great numbers, giving rise to characteristic blood changes. That many cases correspond

with this conception is still admitted to be the case, but further study of the histology of the marrow has brought out the following facts:

1. In most, if not in all, cases of "lymphatic" leukemia the marrow is more or less completely transformed into "lymphoid" tissue, *i. e.*, into tissue substantially identical with that found in the lymphatic glands.

2. There is no reason to believe that this change is due to metastasis from the glands, or that it is secondary to the glandular changes.

3. A considerable number of cases have been reported in which, although the blood showed the changes characteristic of "lymphatic leukemia," there was no enlargement of the lymphatic glands nor of the spleen, the changes being confined wholly to the marrow.

4. In some of these cases glandular hypertrophy appeared late in the course of the disease.

All these considerations have usually been adduced as proof that the marrow changes are always the starting point and essential feature of the disease, both in the "lymphatic" and in the "splenic myelogenous" forms of the disease. It seems, however, more reasonable to conclude (especially in view of certain other facts soon to be mentioned) that the *whole hemopoietic system*—marrow, spleen, and lymph glands—*is involved in every case of leukemia*, the changes preponderating sometimes in the marrow and spleen, sometimes in the glands.

In support of this view we may adduce all the facts above mentioned, facts tending to show that the marrow is more or less involved in every case of the "lymphatic" as well as of myeloid type, and also the following:

1. Careful examination of the lymph glands in cases of the "splenic myelogenous" type show that although these glands are rarely much enlarged, many of them exhibit, on histological examination, essentially the same structure which is found in the marrow.

2. The enlargement of the spleen, an organ which is, on the whole, nearer to the glands than to the marrow, although sharing some of the characteristics of each, occurs not only in the "splenic myelogenous," but also in many cases of the more chronic and some of the more acute types of "lymphatic" leukemia.

3. There are on record a few cases of chronic "lymphatic leukemia" in which the marrow changes were absent or very slight, and at the other extreme some cases of "splenic myelogenous" leukemia show very slight degrees of myeloid transformation in the glands.

The result of these considerations seems to be this: The leukocytic hyperplasia, which in all cases of leukemia is the essential change in the hemopoietic system, may begin in any part of that system, in the glands, in the marrow, perhaps in the spleen, just as amyloid or fatty metamorphoses may begin in any part of the liver. Yet we do not on this account say that the disease in one part *caused* the disease in another. It *sprang up* first here, later there—that is all. So in hemopoietic tissue, although separated in many parts of the body, in bone and spleen, in definite macroscopic lymph glands, and in the interstices of other organs, wherever the lymphatics extend, a hyperplasia may spring up. If it grows slowly it remains more or less localized at its starting point and the symptoms are mild, as in "chronic lymphatic leukemia." If it chances to start in the

marrow and to be of the "lymphoid" type, it runs a quicker course and may kill the patient before it has had time to get under way in the spleen and glands. If it lasts long, all the hemopoietic tissues will be more or less involved. Probably the disease is never strictly local and never as widespread as it might be. It is a matter of degree.

That the hemopoietic system is essentially one and not sharply differentiated into lymphoid and myeloid elements is the postulate of the above conception of the leukemic process. This same postulate of the *underlying unity* of these spatially separate and morphologically differentiated parts (marrow, spleen, and glands) makes intelligible the "myeloid" transformation of glands in the "splenic myelogenous" cases and the lymphoid transformation of the marrow, in the "lymphatic" cases.

Hemopoietic tissue in embryonic life is far less differentiated. Red-cell formation is not confined to the marrow but is shared by the liver, spleen, and by some at least of the lymph glands. Indeed, in some of the lymph glands, especially in those along the vertebral column, red-cell formation appears to last on into adult life. The specialization is considerable, but not complete. Again, there can be no doubt that the marrow is concerned in the production of almost every type of leukocyte found in the blood, and although it is doubtful whether any considerable number of small lymphocytes are normally formed there in the healthy adult, there is no doubt that it is very prone to revert to a "lymphoid" type of cell formation when thrown out of its normal working by diseases of various kinds (smallpox, typhoid, pernicious anemia, as well as leukemia).

Reversion to a less specialized type of cell formation results, if the marrow type prevails, in bringing the spleen and glands into line, *i. e.*, in general myeloid tranformation more or less widespread. If the lymphoid type prevails the marrow is brought into line with the lymph glands. In either case *differences tend to disappear, identities to be accentuated*, sometimes one, sometimes another part of the hemopoietic system prevailing over the rest. This explanation is more in harmony with the facts than any theory of a metastasis or transplantation of marrow cells into the glands or of gland cells into the marrow.

Despite the essential and fundamental identity of all forms of leukemia, the cases divide themselves conveniently into three groups: 1. Myeloid leukemia. 2. Lymphoid leukemia. 3. Atypical leukemia.

Myeloid Leukemia.—Etiology.—The disease is a rare one, fully five times as rare as pernicious anemia and about as rare as myxœdema. Practically nothing is known as to its cause. It certainly has no known relation to inheritance, to the climacteric, to previous hemorrhages, to malaria, or to injury. It is nearly twice as common in males as in females. Of our 87 cases, 54 were in males and 33 in females. The disease occurs most often between the thirtieth and the fiftieth year; thus of 89 cases in this series, 53 occurred between thirty-one and fifty. After sixty it is distinctly rare, only 1 case of this series being beyond that age. Before the twentieth year it is uncommon, distinctly more uncommon than the lymphatic form of the disease. There were 17 cases of this series between twenty-one and thirty years of age, only 9 before the twentieth year. It is a fact of some interest that among the cases occurring in young persons

the female sex predominates, as it does in pernicious anemia, although in the whole series males were very much more numerous. There is no reason to believe that the disease has any special relation to race, season of the year, occupation, or place or residence. Although the possibility has been often suggested that the disease is due to an infection, there is as yet no definite evidence that this is true, and the weight of probable reasoning inclines us against this hypothesis and in favor of a close relationship to the neoplasms.

Pathology.—There are no important lesions other than those of the blood-making organs. Hyperplasia of the leukocytic elements of the bone-marrow with myeloid transformation of the spleen and of the whole lymphatic system to a lesser extent, intracapillary myeloid infiltration (intense and widespreading in the liver, less marked in the lungs), such are the essential lesions of the disease.

The Spleen.—Myeloid transformation of the organ goes on unchecked in most cases, obedient to that mysterious stimulus which calls the whole blood-making system into unnatural activity, and since the spleen is not hindered (as the bone-marrow is), by definite limitations, it may grow larger and larger almost to the time of death. Spleens weighing 4000 to 5000 and even 7000 grams are on record. Despite the enormous increase in its size, the spleen usually preserves quite faithfully its normal shape. Its surface is usually smooth, hard, and coated or mottled with gray or grayish-white areas of fibrous tissue, due to that perisplenitis which is almost always present to some degree, usually binding the organ firmly to the diaphragm and abdominal walls or to adjacent organs.

The gross appearances of the section surface depend largely upon the amount of fibrous tissue present. If sclerosis is extensive, the organ is converted into a tough, grayish mass which creaks under the knife. Where there is but little fibrous tissue the organ has a grayish-red tint more or less mottled with lighter gray and darker red areas. The consistency of spleens of this type is much softer than the fibrous type, although usually somewhat harder than the normal spleen. Areas of hemorrhage or infarction are sometimes present.

Microscopic Appearances.—The organ is converted into a tissue so closely resembling the marrow that the two might be easily mistaken for each other. The Malpighian follicles are practically gone; their place is taken by masses of leukocytes packed together with scarcely any recognizable connective tissue intervening, but channelled here and there by capillaries and sinuses recognizable by their lining of definite endothelium and by the larger number of red cells which they contain when compared with the surrounding tissues. Among the cells which make up the great mass of the organ we find most frequently myelocytes, then polynuclear leukocytes and transitional neutrophiles, and lastly the other granular varieties. Much less common are the non-granular mononuclear cells. A number of nucleated red cells, somewhat greater than in the circulating blood, is usually to be found in the spleen. Almost the only other cell is the megacaryocyte of the marrow, which is fairly common and usually contains cellular inclusions. The amount of pigment and cellular debris seen in a healthy spleen is conspicuously diminished.

In cases in which the amount of stroma is increased we see the bands running especially along the sinuses and capillaries. In these cases, which usually represent more advanced stages of the disease after grave anemia has developed, macrophages are found in considerable number. The cells are crammed with masses of iron-containing pigment, which sometimes hide the nucleus. These cells also contain leukocytes and fragments of nuclei.

This type of disease represents the combination of three processes: (*a*) myeloid infiltration, (*b*) hemolysis, and (*c*) sclerosis. The development of the latter element may be so great that it overshadows all the others, as is not infrequent when the disease has existed for several years. We then find that the organ has become much lighter, sometimes only one-third the average weight of the leukemic spleens. The cellular elements are reduced to one-third or one-fifth of their ordinary bulk. The changes are identical with those above described, but the number of bands of connective tissue passing about the capillaries and sinuses becomes greatly increased. This sclerosis limits the amount of myeloid change, and thus by checking the disease process prolongs the life of the patient. It seems reasonable to explain the sclerosis as an attempt to combat the disease or at any rate to limit its progress.

The Bone-marrow.—The bone tissues are practically unchanged; the most striking change is the banishment of fat and its replacement by a grayish-white, tough cylinder of tissue which can sometimes be turned out without breaking. After exposure to the air it takes on a redder tint, and in the ribs it is always redder than in the long bones. The changes are for the most part similar to those just described in the spleen, but in addition to these the number of megacaryocytes and their size is greater than in the spleen. We find a much larger number of non-granular mononuclear cells (undifferentiated? primordial?), although these cells are less numerous than in the marrow of many cases of infectious diseases or of pernicious anemia. Very many of the myelocytes are in process of division. Nucleated red cells are plentiful, although much less numerous than in pernicious anemia. The number of fully developed red cells is small and contained mostly within the sinuses. There are relatively few macrophages and slight evidences of hemolysis.

Lymphatic Glands.—Rarely is any gross enlargement to be found in the peripheral groups. The intra-abdominal glands are found slightly enlarged, and sometimes attain the size of a walnut. Microscopic examination shows that some of the glands are perfectly normal, others partly transformed into myeloid tissue, while others are almost entirely myeloid in character. The number of megacaryocytes is larger than that found in the spleen and distinctly comparable to the number seen in the marrow. Evidences of leukolysis are abundant, but there is only a little iron pigment or other evidences of erythrolysis. Ocasionally there is some myeloid change demonstrable in the tonsils, Peyer's patches, the intestinal follicles, and in the connective tissue of the omentum.

The Liver.—Great enlargement is the rule; the organ often weighs from 5000 to 6000 grams. It is grayish-yellow in color, homogeneous, and without much indication of the normal markings. The essential histo-

logical change is a stuffing of the capillaries with leukocytes similar to those in the spleen and marrow. The crowding is so great that the normal liver cells, pushed to the wall, atrophy and disappear in large numbers. There is little if any infiltration outside of the capillaries, and the areas, which appear at first like solid leukemic tumors, are in fact bunches of capillaries which have coalesced after the disappearance of the liver cells driven out of existence between them. Within the capillaries the number of red cells is much smaller than in the peripheral vessels. Considerable amounts of iron pigments are to be found, especially in long-standing, anemic cases.

The Lungs.—Since the blood after leaving the spleen and the liver goes straight to the lungs, it is natural that the greatest myeloid infiltration (after that in the organs just mentioned) should occur in the lungs. The conditions are practically the same as those just described in the liver, although much less in degree. Here, as in the liver, the capillaries seem to contain far more white than red cells. The air spaces are encroached upon by the distended capillaries, and the circulation is thus impeded.

Symptoms.—*Mode of Onset.*—The patient usually seeks medical advice because he has noticed on the left side of the abdomen *an enlargement, which is in fact the spleen.* In 32 (or over one-half) of the 61 cases, splenic pain with enlargement or splenic enlargement without pain, brought the patient to his physician. A simple enlargement without pain is twice as common as enlargement with pain (22 cases to 10 cases). About one-third (21 out of 61) of the patients are first made aware of their illness by a *loss of weight and strength.* In 5 cases of the series *fever or chill* was the first symptom, while in 3 cases the disease was ushered in by *diarrhœa.*

Later Symptoms.—For many months the patient may experience no further discomfort. In most cases there is a gradual loss of flesh and a certain amount of inconvenience from the weight of the spleen, which drags upon the ligaments and stretches the adhesions which join it to surrounding structures. Yet many patients feel perfectly well, and no doubt there is in most cases a long latent period during which the patient is actively at work, although the disease is steadily progressing. We get the impression certainly that most of our cases have existed for months or even years before the patient consults a physician. A few rare cases are on record in which hemorrhage, even fatal, has been the first sign of the disease, but, as a rule, such *hemorrhages* as occur are moderate in degree and come later in the course of the disease. Out of 66 cases with good notes upon this point, 52 showed *hemorrhage* at one or another period of the disease. Nosebleed is the commonest form of bleeding, and occurred in 17 of the series. Retinal hemorrhage was found in 7 cases, bleeding from the bowels in 6 cases, and bleeding from the gums in 5 cases. Blood appeared in the urine in 5 cases, and under the skin in 4 cases. There was uterine hemorrhage in 3 cases, gastric hemorrhage in 2 cases, pulmonary hemorrhage in 1, while in 1 case sudden death occurred from cerebral hemorrhage in a patient previously in good health. Yet despite the fact that five-sixths of the cases show *hemorrhage* at some time, it *is rarely a prominent symptom. Rapid loss of weight* occurred in practically every case although the patients did not often complain severely of it.

Gastro-intestinal disturbances are troublesome only in the latter stages of the disease, when marked anemia has supervened. Only 10 of the patients were altogether free from gastro-intestinal symptoms. Yet, as a rule, they did not cause much suffering, Nausea and vomiting were noticed in 32 cases, lack of appetite in 13, diarrhœa in 34, constipation in 22, and flatulence in 9. Occasionally the diarrhœa is early and obstinate.

Respiratory symptoms are limited almost entirely to *dyspnœa*, which is presumably to be explained by the leukocytic overcrowding of the pulmonary capillaries and a consequent encroachment upon the breathing space. As to the result of this, there is usually some pulmonary œdema in the latter part of the disease, and not infrequently an *effusion* occurs *in one or both pleuræ*, especially in the left—a localization for which the proximity of the spleen is probably responsible. As a result most patients are troubled more or less in the latter part of the disease by *cough*, but it is not at all a prominent symptom.

In a few patients much distress is caused by *deafness* due to a leukemic infiltration of the labyrinth. Deafness (presumably of this type) occurred in 6 cases of this series. Difficulty of vision is seldom complained of (only in 6 cases of this series), although retinal hemorrhage is relatively common.

Priapism due to leukemic infiltration or thrombosis of the corpora cavernosa has been repeatedly mentioned in literature, but did not occur in any of the 89 cases of this series. Owing to the great increase of the excretion of uric acid, now and then a patient suffers from gravel or from stone in the kindney.

The nervous system shows practically nothing, although the occasional occurrence of facial paralysis or of neuroretinitis has been noted.

Fever was present at some time in practically every case (88 out of 89) in this present series. As a rule it ranges under 102°, and persists for a few weeks at a time in the more advanced stages, but in 28 cases of this series the temperature reached above 102° and in 6 above 104°.

Anemia.—In the early stages of the great majority of cases there is little or no anemia and the patient has no symptoms referable to it, but before the fatal termination in at least two-thirds of all cases anemia causes considerable suffering. The symptoms are those ordinarily noted in anemia from other causes, namely, muscular weakness, shortness of breath, gastro-intestinal disturbances, œdema, vertigo, and attacks of faintness.

Physical Examination.—In early cases the most striking feature is the *enlargement of the spleen*, which is usually very considerable even when the patient first consults his physician. In 85 out of our 89 cases the spleen reached the level of the navel or lower. In 3 cases it is noted as "palpable" only; in one case it reached only two fingers below the margin of the ribs. In 13 cases it reached to or slightly below the level of the navel. In about one-half of the cases (32) it extended to the crest of the ilium, and in a slightly larger number (37) it extended to the pubes. These figures represent the state of things as ordinarily found and usually described. The surface of the organ is ordinarily smooth and hard; it was so in nearly every case of the present series. On the upper or median edge one or more deep notches are usually to be felt. One distinguishes the organ as the spleen and nothing else, largely by its shape, which, de-

spite its great enlargement, is strikingly well preserved. Its flattened shape and sharp edge contrast, as a rule, with the rounded, shelving, edgeless contour of tumors arising from the kidney. Inflation of the colon further serves to distinguish a kidney tumor from an enlargement of the spleen.

The splenic enlargement may go on progressively until the death of the patient, but if an overgrowth of fibrous tissue occurs in it, the increase in size may be checked, simultaneously with a check in the increase in the number of white corpuscles. The organ may then become smaller, especially in the most chronic cases, but still, as a rule, it preserves its characteristic shape and smoothness of surface. Sudden enlargement of the spleen may be the result of hemorrhage into its substance, while sudden diminution in its size may follow infectious disease occurring as a complication, or result from an attack of diarrhœa. Such diminution in size also occurred in the periods of general improvement, whether these occurred spontaneously or as a result of infectious disease or *x*-ray treatment. Rupture of the spleen with immediate death occasionally occurs, as in the case reported by Joseph L. Miller.

The liver is almost invariably enlarged; only in 3 out of 58 cases of this series was no enlargement found. In the majority of cases in this series it extended from one to four fingers' breath below the ribs, but in 16 cases (or slightly more than one-quarter) it reached the level of the navel and in 4 cases it extended from one to three fingers' breadth below this point.

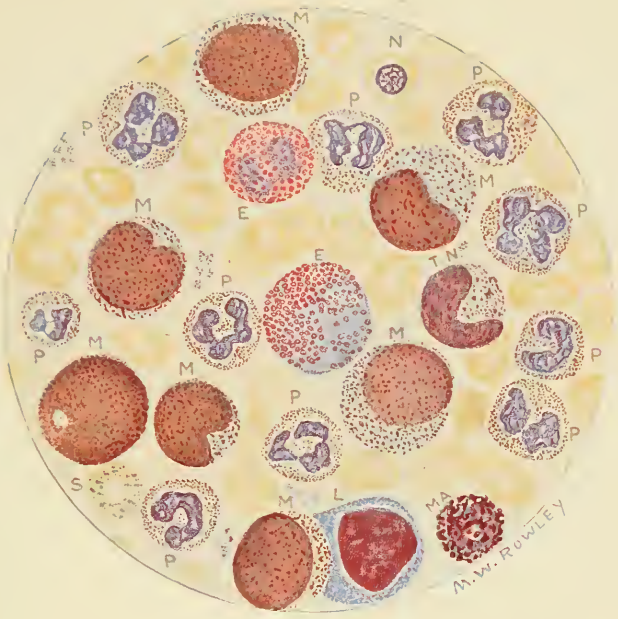
The superficial lymphatic glands are very often as palpable as they are in health, but rarely are they considerably enlarged. Thus, in this series, out of 61 cases carefully examined with reference to this point, 10 showed no glandular enlargement, 45 showed only such slight enlargement as is frequently found in healthy persons, and only 6, or less than 10 per cent., showed marked increase in size. The glands are felt with about equal frequency in the neck, the axillæ, and the groins.

Eyes.—In 2 cases of this series a unilateral exophthalmos was seen, presumably due to leukemic infiltration or hemorrhage into the orbit. Optic neuritis was seen in 2 cases, œdema of the disk in 1 case, and retinal hemorrhage in 7 cases out of 17 examined in the early stages.

Urine.—The most striking and important feature is the great excess of uric acid due to the breaking down of nuclei from the death of white cells. In no other disease is so great an increase of uric acid regularly found, and it is an interesting fact that most of the symptoms often attributed to an excess of uric acid in the system are not found in leukemia. The occasional occurrence of renal stone or gravel has been noted. Gouty manifestations do not occur, so far as known to the writer. Aside from this change there is nothing of importance. In 26 out of 56 cases in this series (or about 50 per cent.) albumin without casts was found, and in 16 other cases albumin with casts appeared. In other words, 75 per cent. of the cases showed albumin or casts, or both.

Blood.—The enormous increase in the white cells is naturally the first point of interest. As a rule, the case is "full blown" from the start; that is when the patient first comes to us the myeloid hyperplasia, and the resulting enormous increase in the number of circulating leukocytes, are already established. In 71 cases with careful records, the average number

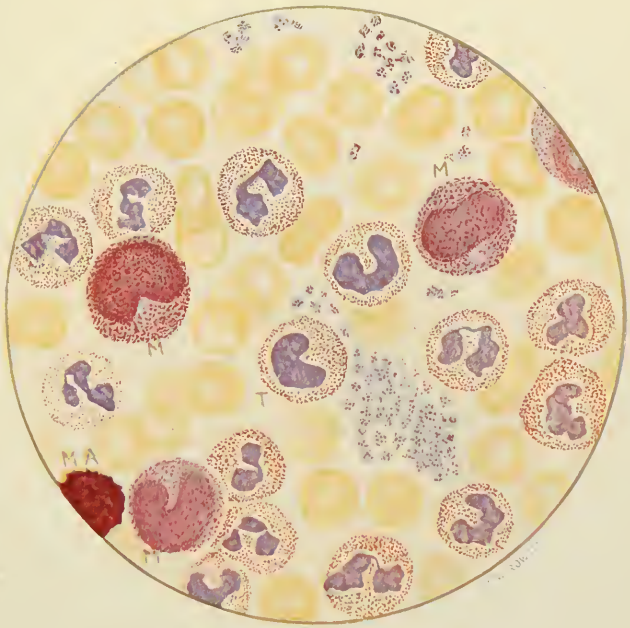
FIG. 1



Myeloid Leukæmia.

Copied from an actual field: *P*, polynuclear neutrophilic leukocytes; *M*, neutrophilic myelocytes *T N*, transitional neutrophile; *M A*, mast cell; *L*, "marrow lymphocyte;" *E E*, polynuclear eosinophiles; *S*, "stippled" erythrocyte; *N*, normoblast.

FIG. 2



Myeloid Leukæmia after X ray Treatment.

Fourteen typical polynuclear neutrophilles; *T*, rather atypical myelocytes; *M A*, mast cell; *T*, transitional neutrophile. Excess of blood platelets.

of white cells was about 410,000 per cmm., at the time when the patient first felt sick enough to consult a physician. Most cases range between 100,000 and 500,000. In 46 of the series the count fell within these figures, yet higher counts are not unusual; 13 cases ranged about 700,000 and 5 reached above 1,000,000. In these 5 cases the actual counts showed respectively 1,554,000, 1,493,000, 1,328,000, 1,072,000, and 1,046,000 cells per cmm. At the other extreme are 5 cases in which the count reached only from 60,000 to 100,000.

The patient's symptoms and the gravity of the disease are not accurately measured by the degree of increase of white cells. Some patients with a relatively low count feel much worse than others with a much higher count, yet in a general way it may be stated that the higher the count the worse the patient feels, and that in most, although not in all, cases a fall in the count is accompanied by an improvement in all the other symptoms.

The increase of white cells is made up chiefly of the ordinary varieties seen in normal blood. The abnormal cells, chiefly *myelocytes*, range usually between 30 and 50 per cent. It is rare to find more than 50 per cent. and not at all infrequently the myelocytes fall below 30 or even below 20 per cent. (6 cases out of 53 of this series). (See Plate XII, Fig. 1, M.)

About equal in number, or slightly more numerous, are the *polynuclear neutrophilic leukocytes*, which in 70 per cent. of the series made up between 30 and 60 per cent. of all the leukocytes present. It should be realized that this means an enormous absolute increase in the number of these cells in the circulating blood. We are apt to think of the blood in leukemia as if its abnormal richness in white cells was owing chiefly to the presence of myelocytes, but, as a matter of fact, the percentage of polynuclears is usually larger and their absolute increase over their normal number is enormous—not less than forty-fold. In 8 cases of this series the polynuclear cells were relatively as well as absolutely increased; in 3 cases they ranged between 70 and 80 per cent. Rarely (only 8 cases of this series) do they fall below 30 per cent. All these percentages of polynuclear neutrophiles would probably be increased if we did not make the attempt to distinguish what are called "*transitional neutrophiles*," forms intermediate between the myelocytes and the polynuclear cells and usually making up at least 7 per cent., often more, in our differential counts. (See Plate XII, Fig. 1, T.N.)

Another point on which special emphasis should be placed is the increase in the actual number of *lymphocytes*, including both the smaller and larger varieties. While it is true that small lymphocytes are occasionally absent, or very scanty (as in 6 cases out of 50 in the present series), they are usually present (from 1 to 5 per cent.), and these percentages when reduced to the absolute number of cells per cubic millimeter represent a considerable increase over the number of lymphocytes in the normal blood. What has just been said of the small lymphocytes applies with more force to the larger forms, the non-granular mononuclear leukocytes, to which so many different names have been given. Of these forms between 3 and 30 per cent. are usually present. In only 16 of the cases did they fall below 3 per cent., while in 2 cases they rose (near the time of death) above 30 per cent. They are of special significance in relation to

the problem of the two forms of leukemia and their relation to each other. (See Plate XII, Fig. 1, L.)

Mast cells are almost always greatly increased. In two-thirds of the cases of this series they ranged above 3 per cent., and in one-third of the cases above 5 per cent. Twenty per cent. is the highest observed by the writer, although others have noted much larger numbers. (See Plate XII, Fig. 1, M. A.)

The number of *eosinophiles* is almost always increased if we fix our mind upon absolute numbers and not upon percentages. The misunderstanding of Ehrlich's original dictum upon this point has now apparently been removed, as we have come to comprehend that he was speaking of actual numbers and not of percentages. Even in percentages fully one-half of our cases ranged above the normal. A small percentage of the eosinophiles, usually between 0.5 and 5 per cent., are mononuclear, and have received the name of *eosinophilic myelocytes*. They are not peculiar to this disease, although rarely seen in such numbers in any other.

The cells of the different types vary more or less from their normal morphology in most cases of leukemia; the polynuclear cells are often much undersized, less often gigantic. The number of granules which they contain is sometimes very much reduced, and occasionally no granules at all can be made out. This is usually in the severest cases or near the fatal termination. In the lymphocytes the number of "azur" granules is often considerably greater than the normal, and is sometimes so great that we find it difficult to distinguish these cells from ordinary myelocytes, especially as the granules exhibit every gradation in tint from the brightest crimson to the darkest blue. The occurrence of considerable numbers of supposedly "primordial" cells has been noted. In the eosinophiles we find the same abnormal types referred to in the neutrophiles, viz., dwarf cells, giant cells, and abnormal scantiness of granules. Occasionally there are present in the same cell granules which, judging from their color and size, appear to belong to very different types.

Red Cells.—The fact that *anemia is a relatively late complication* and not an early or necessary symptom of the disease has been mentioned. In 5 cases of the present series the number of red cells was practically normal when the patient first came under observation, and in almost one-half of the cases the anemia was slight or moderate (3,000,000 to 5,000,000 cells per cubic millimeter). Sooner or later, however, grave anemia almost always supervenes, and in 36 cases out of 61 in the present series the red cells were between 2,000,000 and 3,000,000 when the patient was first seen. Even lower figures (1,000,000 to 2,000,000) are recorded in 9 cases, but all of these were late cases. On the other hand, it occasionally happens that the patient lives for years, and even approaches the end of his life, with very slight anemia. This was true in 4 cases of the present series. When remissions occur, whether spontaneously or as the result of infectious disease or *x*-ray treatment, the patient's improvement usually runs parallel with a gain in the number of red corpuscles, and in favorable cases the anemia may almost altogether disappear and remain absent for considerable periods.

The *color index* is usually low, as in 60 out of 69 cases of this series. In 6

cases it was high and in 3 normal. In other words, the type of anemia usually corresponds, in this respect as in most others, to the ordinary secondary or symptomatic type. The individual red cells are usually small, pale and moderately deformed, the degree of these changes depending upon the severity of the anemia.

Nucleated red cells are invariably present, *even in the absence of anemia.* Indeed, they may be as numerous in the cases without anemia as in anemic cases. As a rule, both the larger and the smaller varieties are present. Thus, in all the 47 cases of this series, in which special attention was paid to this point, normoblasts were present, and in all but 4 of these same cases megaloblasts were also present. In two-thirds of the cases (24 out of 34) the normoblasts were in excess, while in 10 cases the megaloblasts predominated. In practically every case the number of *blood plates* is greatly increased.

Differential Diagnosis.—Few diseases are so easy to recognize. The presence of an enlarged spleen leads to a blood examination, and thus in 99 per cent. of cases to a rapid and accurate diagnosis. Only gross negligence or ignorance can lead us astray. The writer twice found sarcoma of the left kidney with enormous polynuclear leukocytosis in patients previously supposed to have leukemia. Twice he has seen a surgeon cut down on a leukemic liver, but only because he was bound to make his diagnosis by operating, and disregarded the obvious facts which blood examination had previously revealed. During the stage of remission, when the blood has returned to normal, diagnosis may be impossible, but the history usually prevents mistakes. A number of rare atypical forms of the disease present difficulties—even insuperable ones—in classification *intra vitam*, but as such are very rare and almost invariably run the same course as ordinary leukemia, their precise title is not of great importance.

Course, Duration, and Prognosis.—Almost invariably the disease pursues a chronic course. In the whole literature not more than a dozen cases are on record in which the symptoms may be properly called acute. In this series only 10 out of 84 cases lasted less than six months, even if we accept at its face value the patient's statement as to the duration of his disease before he consulted his physician. Most cases last from one to three years (42 out of 84 in the present series); 14 of the cases lasted more than three years, and 28 less than one year. Very frequently the disease remains latent, that is to say, produces no considerable discomfort for many months, and although the patient is aware that he has an enlarged spleen he does not consult a physician. But at any time in the course of this apparently latent disease an acute, even fatal, aggravation may take place, and in carelessly recorded cases these acute terminations of chronic cases are first spoken of as "acute cases."

In an uncertain but probably rather small percentage spontaneous remissions occur and both blood, spleen, and all the other tissues may return, so far as we know, to the normal. The same thing may occur as a result of any of the infectious diseases presently to be mentioned as complications. Sometimes such remission occurs during the administration of arsenic, possibly as its result. There is no doubt, however, that as a result of *x*-ray treatment a great improvement does occur in most cases.

There is no possibility any longer that this improvement should be looked upon as a coincidence, yet, so far as we can say, up to the present time true recovery is unknown.

Complications.—Infection by pyogenic organisms occurred in 15 cases of the present series. Among these 15 cases there were 3 of erysipelas, 2 of carbuncle, 3 of terminal streptococcus sepsis and various local abscesses. Next to the pyogenic infections, tuberculosis is probably the most common complication. The miliary form is most often seen, but ordinary chronic pulmonary tuberculosis also occurs. Pneumonia not infrequently occurs, and like other infections may bring about a temporary amelioration in all the symptoms. The same is true of such complications as rheumatic fever, influenza, and typhoid. As a rule these complications produce a rapid fall in the number of white cells. Sometimes this is accompanied by an improvement in all the symptoms, but sometimes these go on unchecked. Occasionally the blood count is not affected or rises still higher than during the occurrence of the complications.

Lymphoid Leukemia.—Conditions of Occurrence.—Nothing of importance is known as to the cause of the disease. It is distinctly more rare than myeloid leukemia. Thus during twelve years the writer has seen 89 cases of myeloid leukemia and in the same period only 51 cases of lymphoid leukemia.

Age.	Cases.	
2 to 4 months	5	25 acute cases, (3 weeks to 3 months).
1 to 10 years	3	
11 to 20 years	5	
21 to 30 years	12	
31 to 40 years	4	(2 acute, 2 chronic).
41 to 50 years	6	(3 acute, 3 chronic).
51 to 60 years	7	13 chronic cases, (6 months to 4 years).
61 to 70 years	4	
71 to 80 years	2	
Total	48	

The irregular distribution of the cases suggests that we are dealing with a mixture of two or more sub-types, and a closer analysis of the cases shows this to be true. One type of the disease—the acute form—is much more common before the thirty-first year than after it (22 cases under thirty-one, 5 cases over thirty-one years), while the *chronic* form of the disease is represented in this series *wholly* by cases occurring in persons *over* thirty-one years of age. There were 18 chronic cases, 13 of which (or nearly 80 per cent.) occurred in patients over fifty-one years of age, while not a single acute case occurred after the fifty-first year.

Sex.—There were in the series 31 males and 14 females, while in 3 of the infants the sex was not recorded. The disease is much more common in males, as is shown by all statistics. Race, residence, occupation, season, seem to have no relation to the disease.

Symptoms.—*The onset* may be acute and stormy or gradual and insidious. Acute cases usually begin with weakness and fever; sometimes, however, there is glandular enlargement (as in most chronic cases) pre-

ceding the appearance of any other symptom. Combining both types—the acute and the chronic—we find the following modes of onset:

	Cases.		
With enlargement of glands	20		
With weakness and pallor	15	21	41 cases.
With fever	6		
With abdominal pain and swelling	3	6	
With enlargement of spleen	3		6 cases.
With hemorrhage	1		

In the chronic cases the *glandular enlargement* may last almost unnoticed for years, until the comment of a friend or some trifling digestive or respiratory disturbance brings the patient to a doctor. In acute cases the enlargement may be rapid, but in the most acute of all there is often no enlargement externally, the disease being confined to the marrow and internal glands, or wholly to the marrow.

Weakness and dyspnœa on exertion are present (*a*) in the cases with fever, and (*b*) in the cases with anemia; that is, chiefly in the acute cases or in late stages of any case. The evidences of anemia appear, as a rule, earlier than in the myeloid form of the disease. Thus in 34 cases the writer found marked anemia at the first examination of 30, or nearly 90 per cent., while only 4 cases were recognized some months or years before there was any anemia. The *anemia* manifests itself by pallor, mental and muscular weakness, dyspepsia and constipation, dyspnœa and œdema of the feet, headache, vertigo, and tinnitus. The degree of anemia was marked in 34 cases, moderate in 1 case, and slight or absent in 10 cases.

Gastro-intestinal troubles are, on the whole, slight. Short periods of nausea and vomiting were present in 15, or about one-third of the cases, many of them febrile ones. Anorexia was complained of by only 11, dyspepsia by 7, constipation by 14, and diarrhœa by 7. The *cardiac and respiratory* symptoms are simply those seen in all anemias. In the chronic non-anemic cases they are absent. Occasionally a pressure cough, due to enlarged bronchial glands, gives much suffering. *Hemorrhages* are considerably more common than in myeloid leukemia, but are confined chiefly to the acute cases. Among 34 cases examined with reference to this point there were subcutaneous hemorrhages in 17 cases, hemorrhage from the gums in 15 cases, blood in the urine in 8 cases, blood in the vomitus in 3 cases, blood in the feces in 3 cases, and blood in the sputum in 4 cases. *Retinal hemorrhages* were found in 8 out of the 9 cases examined.

Physical Examination.—Many cases are first discovered in the course of a routine physical examination. *Glandular enlargement* is the most striking feature. As a rule, the glands of the neck, axillæ, and groins are all affected (44 out of 46 cases), the kernels averaging from 0.5 to 2 cm. in diameter. They are discrete or loosely joined in small groups, usually hard, rarely tender, and movable under the skin. Large masses such as are the rule in Hodgkin's disease are never seen. They rarely attract the notice of the passer-by and seldom give rise to pressure symptoms. The relative frequency of involvement is shown by the following figures: glands in the groins, 44 cases; glands in the axillæ, 43 cases; glands in the

neck, 41 cases; tonsils enlarged, 7 cases; epitrochlears, 4 cases; and the abdominal glands palpable in 2 cases.

Splenic enlargement, although much less marked, on the whole, than in myeloid leukemia, is present in almost every case. In 34 out of 41 cases in the series the organ was easily felt, and in several of the other cases (seen but once) it was doubtless palpable at subsequent examinations. The characteristics of the organ are essentially those described under myeloid leukemia. The *liver* is less often demonstrably increased in size; the notes of 34 cases showed that it was enlarged in 25.

Loss of weight is usually marked in acute cases and slight in chronic cases. *Fever* was present in all but 5 of the cases examined. It is sometimes high and continued, so that the diagnosis of typhoid fever is considered or even made, as in 3 of the present series. More often it is irregular and occurs in short periods of five to ten days each. In this series the temperature reached 100° in 4 cases, 100° to 102° in 10 cases, 102° to 104° in 8 cases, and 104° or higher in 9 cases.

Ocular symptoms are rarely marked. The retinal hemorrhage above-mentioned interfered with vision in only 2 cases of the series. As a rule they do not harm. Exophthalmos (unilateral) was present in 1 case; presumably it was referable to leukemic infiltration or hemorrhage in the orbit. *Deafness* (due presumably to leukemic labyrinthitis) occurred in 4 cases.

The urine was normal in only 7 out of 30 cases. In 7 cases it contained albumin, and in 16 albumin with casts, mostly of the hyaline and granular varieties. Blood in the urine was seen in 8 cases, and in some of these it was also adherent to casts. The increase of uric acid is also present in the lymphoid form but as the number of blood leukocytes is less increased, the uric acid resulting from their death is also less increased.

The Skin.—Three types of lesion are important: (1) Ecchymoses, sometimes minute, sometimes extensive; (2) subcutaneous abscesses; and (3) leukemic nodules. Since there are minute collections of lymphoid tissue scattered here and there over almost every square inch of the body, we need not assume any metastases to account for the cutaneous nodules which sometimes develop in enormous numbers. Some cases of this type have been diagnosed as sarcomatosis. A discussion of the relation between sarcoma and lymphoid leukemia will be found on page 679.

The Blood.—The gross appearance of the drop is not at all striking in this or in the myeloid form of leukemia. Its color is dependent on the degree of anemia, and the only suggestion of the leukemic change is in a slightly dull and opaque quality of the usually bright and shining surface of the drop. In the attempt to spread the drop on coverslips the practised hand will sometimes get an inkling of the real condition of things, for the masses of leukocytes make the film thick, viscous, and difficult to spread. The grade of anemia at the first examination of 33 cases is shown in the following figures:

		Cases.
Red cells numbered	5,000,000 to 5,500,000 in	2
" " "	4,000,000 to 5,000,000 in	5
" " "	3,000,000 to 4,000,000 in	7
" " "	2,000,000 to 3,000,000 in	9
" " "	1,000,000 to 2,000,000 in	9
" " "	under 1,000,000	1

The average count is therefore about 2,800,000 at the time when the patient is first seen. In all but the most chronic cases the count of red cells falls progressively until near death, when it is about 1,600,000 on the average. In remissions the count rises rapidly. In 11 cases of this series it averaged 3,900,000 in a remission, but only 2 cases reached 5,000,000 or higher. The reasons for this appear to be two: (1) crowding out of erythroblastic by leukoblastic tissue in the marrow (myelophthisis), and (2) hemolysis. As the multiplication of leukocytes in the marrow reaches large proportions, the lymphoid tissue takes up more and more (*a*) of the space occupied by fat and (*b*) later of the space occupied by young red cells. The marrow can no longer replace the red cells which wear out in use, and still less the increasing number which vanish by hemolysis. Hence, the red cells are slowly or rapidly worn out and anemia results. The *color index* is usually low in all the earlier stages, before the number of red cells has become much reduced (12 cases out of 14). When the anemia becomes grave, the color index is apt to be high (9 cases out of 13). Thus the index was low in 12 out of 14 cases when the red cells were ranging from 3,000,000 to 5,000,000, while the index was high in 9 out of 13 cases when the red cells were ranging from 500,000 to 2,000,000.

The stained specimen shows a varying amount of anemia with more or less achromia, poikilocytosis, abnormal staining, and nucleated red cells. Normoblasts were present in 17 out of 19 cases carefully studied. Megaloblasts were present in 13 out of 15 cases carefully studied. The normoblasts were in excess in 2 cases and megaloblasts in excess in 7 cases.

Leukocytes.—The excess of cells in the peripheral circulation is much less than in the myeloid cases. Whereas in the myeloid cases the average count at the first examination was about 410,000 per cmm., the average in 34 lymphoid cases was 180,000. In 20 cases, or nearly two-thirds of this series, the first count was under 60,000. The following are the figures:

	Cases.
Under 10,000	1
10,000 to 20,000	2
20,000 to 30,000	2
30,000 to 40,000	3
40,000 to 60,000	8
60,000 to 80,000	4
100,000 to 200,000	7
200,000 to 300,000	2
300,000 to 400,000	2
700,000 to 800,000	2
1,505,000	1

As the symptoms are aggravated and the anemia progresses the counts are about as likely to fall as they are to rise. The average count in 17 cases studied near death was only 300,000, yet there were 9 cases, or over one-half, with counts below 80,000.

The highest counts reached in each case are tabulated below:

	Cases.
20,000 to 30,000	2
30,000 to 40,000	1
40,000 to 60,000	4
60,000 to 80,000	4
80,000 to 100,000	1
100,000 to 200,000	7
200,000 to 400,000	4
400,000 to 1,000,000	5
1,631,000	1

From the standpoint of diagnosis the most interesting fact in these tables is the large proportion of low and moderate counts, comparable to the leukocytosis of infectious disease and likely to be overlooked in a hasty examination. Yet it is also true that the highest count in the present series, 1,631,000, is higher than any in the myeloid group.

Differential Count.—The blood film presents the sharpest possible contrast with myeloid leukemia. Myeloid blood shows an almost infinite variety of cell types. Lymphoid blood shows an endless monotony—the same cells in field after field. The writer has counted 1000 cells in successive fields without finding anything but "lymphocytes."[1] In a count of 3500 cells in this case there was 99.6 per cent. of "lymphocytes." This is of course an extreme instance, but it is not at all rare to find that 95 per cent. or more of the white cells belong to a single type, and not a patient in the series had less than 60 per cent. of "lymphocytes."

	Per cent.	Cases.
"Lymphocytes" (large and small)	98 to 100 in	2
" " " "	95 to 98 in	8
" " " "	90 to 95 in	12
" " " "	80 to 90 in	5
" " " "	70 to 80 in	5
" " " "	60 to 70 in	1

Among the "lymphocytes" in these 33 cases the large forms predominated in 14 cases and the small in 19, but in several of these it was difficult or impossible to decide in which group ("large or small") many of the cells belonged. Sometimes a large proportion were about 10μ in diameter, *i. e.*, neither large nor small. (See Plate XIII, Fig. 1.)

Thus far the prevailing cell of lymphoid blood has been referred to as a lymphocyte. In some patients, especially those running a mild chronic course, the cells have all the characteristics of the ordinary small lymphocyte of normal blood. But in many of the acute cases the prevailing cell differs distinctly from both the small and the large lymphocyte. It is difficult to tell whether the cells of lymphoid leukemia differ from *any* of the cells known as "*large mononuclear*" in the terminology of most writers. For among the cells of this type sometimes found in the normal blood are some that correspond with the descriptions and pictures of (1) Türck's "stimulation cells," (2) Nägeli's "myeloblasts," (3) Pappenheim's "splenocytes," (4) Unna's "plasma cells," (5) Weil's "non-granular myelocytes," (6) Cornil's "markcellen," and many others. (See Plate XIII, Fig. 2, L, L, L and A.)

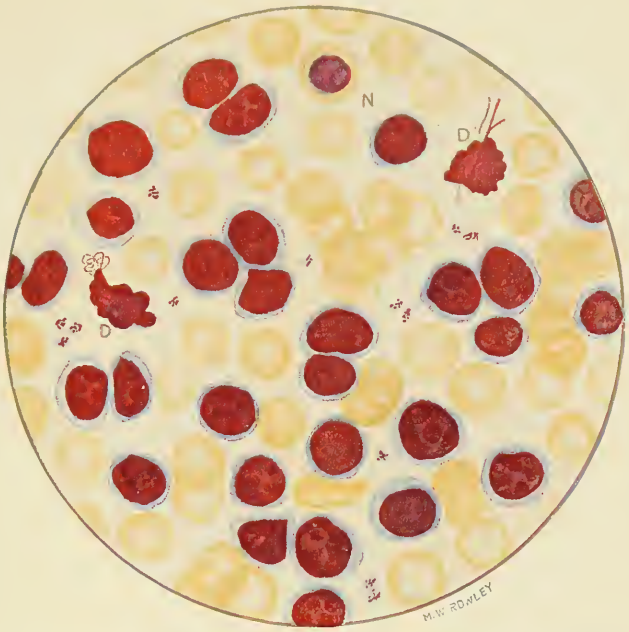
Each of these cells fades by transitional forms: (a) into each of the others and (b) into the large lymphocyte. Hence all that can be said of the atypical non-granular mononuclear cells of lymphoid blood is: (1) That they belong in all probability to a group very near the primordial cells, whence both leukocytes and erythrocytes are derived. (2) That they are probably identical with some or all of the cells above catalogued. (3) That they are probably marrow cells rather than lymph-gland cells.

The Relation of the Type of Cell to the Course of the Disease (Acute or Chronic).—Fränkel first called attention in 1897 to the fact that in acute leukemia the cells were usually of the lymphoid type and usually large.

[1] The sense in which I here use this word is explained below.

PLATE XIII

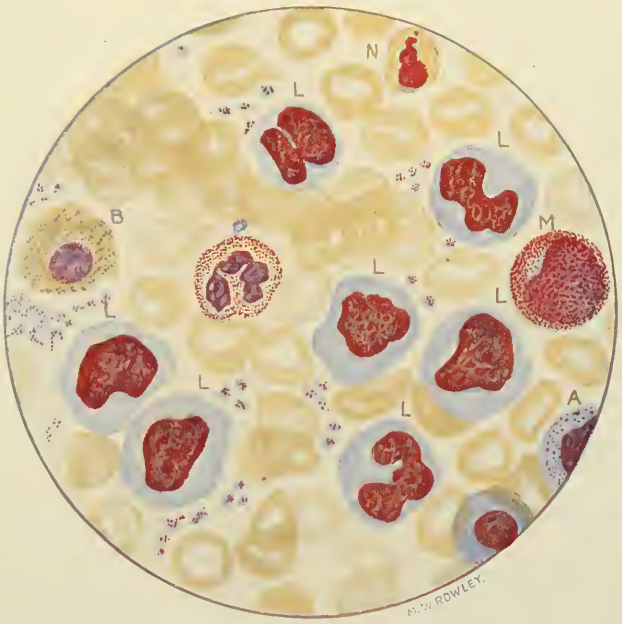
FIG. 1



Chronic Lymphoid Leukæmia. (Actual Field.)

Twenty-nine typical small lymphocytes; *D D*, degenerating lymphocytes; *N*, normoblast.

FIG. 2



Acute Lymphoid Leukæmia. (Actual Field.)

L, atypical "lymphocytes" (Naegeli's myeloblasts); *M*, neutrophilic myelocyte; *P*, polynuclear neutrophile; *A*, "large lymphocyte," with "azur" granules; *B*, megaloblast (stippled); *N*, normoblast

He denied the occurrence of a chronic lymphatic form of the disease, and asserted that all lymphatic cases are acute and all chronic cases myeloid in type. While this statement applies to the great majority of cases of each group, there are many exceptions to it. Cases of acute myeloid leukemia do occur, although they are very rare. Cases of chronic lymphatic leukemia are slightly (but only slightly) less common than cases of acute lymphatic leukemia. In this series, 17 were chronic (6 months to 5 years; average 2 years), 22 were acute (3 to 10 weeks; average 6 weeks), and 5 were subacute (2 to 5 months; average 3 months). The criterion in these (as in almost all the cases on record) is the duration of overt symptoms. Many classed as acute may in fact have represented acute terminal symptoms in chronic cases.

Now, in the study of the size of the "lymphocytes" in 33 of these cases, the large forms were found to predominate in 14, the small in 19; but, as said above, many cases might be transferred from the "large" to the "small" group because (*a*) there are many cases with borderline cells, neither large nor small; and (*b*) in the same case at different times the average size of the cells may vary. In a general way, however, it may be said that the large cells are rarely seen in chronic cases, while in "acute" cases either large, small, or medium-sized cells may be found. This finding accords with that of Gulland and Goodall.[1]

The *polynuclear cells* in lymphoid blood are reduced in a degree corresponding with the increase of lymphocytes. Practically all the cells are either polynuclears or lymphocytes. The *eosinophiles* and *mast cells* are, as a rule, reduced both relatively and absolutely. No eosinophiles were found in 15 out of 28 cases of this series. In 12 cases they varied from 0.1 to 3 per cent., and only in 1 case did they rise above 3 per cent. Mast cells were noted in only 2 cases. Myelocytes were wholly or nearly absent in 17 cases, under 3 per cent. in 9 cases, and between 3 and 5 per cent. in 3 cases. The writer would interpret the presence of myelocytes in these cases (as in pernicious anemia or ordinary leukocytosis) as a "stimulation myelocytosis," and not as a hint of a transition to mixed or myeloid leukemia. *No mixed forms of leukemia* have been seen in the writer's field of work.

Complications.—Tuberculosis (miliary or chronic pulmonary) is not uncommon, but the most frequent interruption of the course of the disease is one or another type of septicemia. Thus, terminal streptococcus sepsis occurred in 5 cases, local abscess in 3 cases, toxemic jaundice in 2 cases, and vegetative endocarditis in 1 case.

Differential Diagnosis.—Like myeloid leukemia, the lymphoid variety is one of the easiest of all diseases to recognize, provided we do not forget to examine the blood. The only cases in which diagnostic difficulties occur are those in which no blood examination is made; such cases are especially those in which the spleen and external lymph glands present no enlargement, cases, in other words, in which the disease is confined to the bone-marrow and internal lymph glands or to the bone-marrow alone. These cases, which are usually of the acute type, are apt to be mistaken for typhoid fever, tuberculosis, purpura, or septicemia.

[1] *Journal of Pathology and Bacteriology*, London, June, 1906.

In the writer's experience there has risen serious doubt in the diagnosis *between lymphatic leukemia and lymphocytosis* in three groups of cases. The first is illustrated by a child aged 12 years with pneumonia. The history was very incomplete and the pneumonia of bronchopneumonic type. The blood showed 94,000 white cells, 75 per cent. of which were small lymphocytes. The writer made the diagnosis of lymphatic leukemia. Within a week the pneumonia had disappeared. Coincidently with this the blood returned to normal, and there has been no return to the leukemic condition. Subsequent investigation showed that the pneumonia had complicated a well-marked case of whooping cough, and there is no reason to doubt that the lymphocytosis was due to this cause.

Following a case of wound sepsis, acquired at autopsy, a physician of my acquaintance had a secondary lymphangitis with swelling of the glands not only on the affected side but in the other axilla. The white cells were increased to between 20,000 and 30,000, but in the differential count the lymphocytes, not the polynuclear cells, as would be expected, were in the majority, and there was serious doubt whether the diagnosis should be wound sepsis or acute lymphoid leukemia. The course was that of an ordinary case of sepsis, at the end of which the blood returned to normal. After tonsillitis a general lymphoid enlargement with lymphocytosis may occur. I have seen 3 such cases mistaken for leukemia.

We have at present no sure method of avoiding such diagnostic errors, but we must remember that very marked lymphocytosis occurs in most cases of whooping cough, not only in the paroxysmal stage, but also in the complications of the disease. It must also be borne in mind that the stimuli (chemotactic?) which ordinarily produce a leukocytosis, in connection with septic lymphadenitis, may result in lymphocytosis; indeed, the wonder is that this is not always the case.

Cutaneous Lesions in Leukemia and Pseudoleukemia.—(1) Lymphoid tumors in the skin. (2) Various reactions of the pruriginous type (prurigo, pruritus, urticaria, eczema). (3) Generalized exfoliative dermatitis (Nicholau).

Cutaneous tumors occur almost exclusively in lymphoid leukemia. So far there is no record of their occurrence in myeloid leukemia, and in pseudoleukemia they are distinctly rare. They are most common about the face, and often ulcerate. Presumably they arise, like many other leukemic lesions, from the minute lymphoid follicles which Ribbert has shown to be scattered so thickly through all tissues. They are usually from 4 mm. to 1 or 2 cm. in diameter. Like other leukemic and pseudoleukemic lesions they may regress and disappear "spontaneously" or as a result of infectious disease or *x*-ray treatment. Histologically they are identical with other leukemic infiltrations.

Sometimes, as a forerunner of leukemic or pseudoleukemic tumors, a variety of itching, eczema-like lesions may occur. Dry, scaling lesions resembling pityriasis—with some prurigo, but without any scar formation or retraction—may be distributed over the whole body. Its evolution is slow, afebrile, with very little infiltration. It is less erythematous than pityriasis rubra, although some authors have also described "pityriasis rubra" in pseudoleukemia.

Features Especially Characteristic of Acute Stages of Leukemia (Acute Leukemia) Myeloid or Lymphoid.—Fever, hemorrhages, rapid rise (or fall) of the number of circulating leukocytes, and rapid changes in the organs affected are the most striking features. The cases are apt to be mistaken for typhoid fever, since they are associated with a high continued fever (101° to 104° or thereabouts), a "typhoidal" or drowsy mental state, enlarged spleen, and perhaps hemorrhage from the bowels. The cutaneous and buccal hemorrhages, with a spongy, ulcerating condition of the gums or tonsillar regions, recall scurvy or purpura hemorrhagica. The drenching sweats, often accompanied by chills, or by enlargement of the liver, have led, in 3 cases known to the writer, to the diagnosis of hepatic abscess; malignant endocarditis or other types of septicemia are also suggested. From all these conditions the blood examination should quickly and surely distinguish the disease.

Prognosis.—Recovery, so far as is known, never occurs. Nearly half of cases are of the acute type and die in less than ten weeks from the onset of symptoms. The chronic cases are less frequent, and may last from six months to five years. The occurrence of fever, hemorrhages, rapid enlargement, and multiplication or disappearance of glandular tumors point to an acute form. If the large forms of lymphocytes predominate in the stained specimen, the disease will probably pursue the acute course, but there are exceptions to this rule. Most chronic cases are associated with excess of small lymphocytes in the blood, but this blood picture is also seen in some of the acute cases.

In the absence of complications, the lower the leukocyte count the better the prognosis, but it should be remembered that in the presence of septicemia or tuberculosis complicating lymphoid leukemia, we often witness a fall in the number of white cells, synchronous with a failure of the patient's strength, so that at the time of death the leukocytes may be normal or subnormal. Other things being equal, the older the patient the better the prognosis. Remissions occur, as has already been said, sometimes spontaneously, more often following arsenical medication or intercurrent infection, and most frequently of all as a result of *x*-ray treatment. With the exception of those produced by *x*-ray treatment, remissions rarely last more than a few months. How long life may be prolonged as a result of *x*-ray therapy we cannot as yet say.

Treatment of Both Forms of Leukemia.—Five years ago the treatment of this disease seemed practically without avail. Today we can assure the patient in the majority of cases—that is, in about two-thirds of all myeloid or chronic lymphoid cases—that very marked improvement will follow the judicious and persistent use of *x*-ray treatment. How long this improvement can be maintained we cannot say. That the treatment reaches the root of the disease does not seem possible but there are today a number of patients kept alive and in comfort for years who show as yet no signs of relapse.

The treatment should be begun as soon as the diagnosis is made, not only in early cases, with relatively mild symptoms, but also in cachectic, febrile, and emaciated patients. Some of the writer's brilliant therapeutic successes have been in cases of this type. As to the details of

treatment, individual operators give different advice. The main point is to put the patient under the care of an experienced operator. Some prefer to give relatively long exposures, and to separate them by intervals of at least a week; while others treat the patient each day, or every other day, with a relatively short sitting. As to the use of hard tubes, soft tubes, deep-penetrating and superficial-acting apparatus, there is difference of opinion.

The spot selected is usually the area corresponding to the enlarged spleen, but most operators expose the epiphyses of the long bones, the liver, or the thorax in a considerable proportion of their treatments. In patients presenting marked glandular enlargements, the enlarged glands themselves should be given exposures.

Results begin to appear usually within a few weeks, and should be very marked within two months. The red corpuscles begin to increase, the number of white cells and the size of the spleen to diminish. As the white cells diminish in number, the differential count also rapidly changes. First, the polynuclear neutrophiles become relatively increased, as the number of myelocytes, eosinophiles and mast cells diminishes. Later, in favorable cases, the differential count may become altogether normal. The number of degenerating cells is largely increased. As the spleen diminishes in size, it becomes likewise softer and more movable. In many cases it recedes altogether out of reach behind the ribs. In glandular cases similar changes occur. The glands become more movable, more discrete, smaller, and may altogether disappear.

When treatment is intermitted, the patient may remain in good health for weeks or months. So far as known by the writer, there are as yet but few cases on record with the preservation of health without treatment for more than a year. Sooner or later, the leukemic changes begin to manifest themselves once more in the blood, and treatment must be resumed or the patient will rapidly lose ground. With the second course of exposures to the *x*-rays the patient's symptoms usually improve as before, but there is unfortunately a not inconsiderable group of cases in which treatment after relapse is unavailing. Sometimes, indeed, the *x*-rays lose power much earlier in the course of treatment; after a temporary improvement the patient begins to run down, and dies before the blood has ever reached normal and without any intermission in the treatment.

After the earlier sittings the patient may feel worse instead of relieved; his fever may rise, his lassitude increase. Sometimes these untoward effects persist as long as the treatment is used and we have to give up this use of the *x*-rays. Such untoward symptoms have been attributed to an auto-intoxication due to the absorption of the products of the leukocytes disintegrated by the action of the *x*-rays. In acute cases, especially of the lymphoid type, the treatment is usually unavailing, and sometimes has seemed to hasten the fatal termination. Animal experiment shows that the *x*-rays have a selective action upon the leukoblastic tissue, and that under their use the spleen, lymph glands, and leukoblastic marrow undergo rapid atrophy.

The *benzol* treatment of leukemia given alone or combined with *x*-ray and arsenic is certainly of some value in prolonging life. Up to January,

1914, about 20 cases are on record since the suggestion of the treatment by v. Koranji in July, 1912. From 3 to 5 grams of benzol a day are given diluted with equal parts of olive oil and enclosed in capsules. Complete symptomatic and hemological recovery may follow (as also after arsenic or *x*-rays) but ten months after the cessation of treatment is, up to date, the period of continuous health. I believe that this treatment, like all hitherto suggested, will prove to be no cure though a valuable palliative and prolonger of life.

Atypical Leukemia.—The most important variations from the types above described are as follows:

1. *Leukemic changes in the hemopoietic system without leukemic blood (pseudoleukemia).*

2. *Leukemic blood without leukemic changes in the blood-making organs (circulating myelomatosis).*

3. *Apparent combinations of leukemia with pernicious anemia (leuk-anemia).*

4. *Tumor-like growths of hemopoietic tissue with or without leukemic blood:* (*a*) Diffuse (chloroma, Sternberg's leukosarcoma); (*b*) Local (myeloma).

Less important are the supposed "mixed forms" of leukemia and the numerous minor variations in the leukocyte formulæ (atypical blood pictures) in otherwise typical cases of leukemia.

1. **"Mixed leukemia,"** part myeloid, part lymphoid, is certainly a great rarity, unless arbitrarily defined. In a series of 140 cases there was none which seemed to the writer to deserve such a title, and the distinction into myeloid (89 cases) and lymphoid (51 cases) was not difficult. Yet cases are often reported as "mixed leukemia," (*a*) through pure misunderstanding of the terms ("mixed-cell" (myeloid) "leukemia" being mistaken for "mixed leukemia"), and (*b*) through unfamiliarity with the fact that in almost all cases of classic *myeloid* leukemia a variable (sometimes considerable) percentage of lymphocytes is present. In some cases this percentage becomes increased (or decreased) toward the end of the disease. Yet it is improper to attribute to such trifling changes the importance implied in stating that the disease has changed from the myeloid to the lymphoid form, or *vice versa*. Cases with high leukocyte counts and considerable percentages of neurophiles (mononuclear and polynuclear), of eosinophiles, and of mast cells should always be classed as myeloid, even when the percentage of non-granular mononuclear forms is also large.

2. **Atypical Blood Changes in Leukemia.**—(*a*) Absence of eosinophiles, of mast cells, or of both. (*b*) Extraordinarily high percentages of one or both of these varieties (20 to 50 per cent.). (*c*) Strikingly high percentages of polynuclear neutrophiles (70 to 90 per cent.), or remarkably low percentages. (*d*) "Plasma cell leukemia," a condition in which a large proportion of the circulating leukocytes are regarded as plasma cells.

3. **Atypical, Sarcoma-like Growth of the Hemopoietic Tissues.**—(*a*) The best-studied examples are those known as *chloroma*. (*b*) Attention has also been called (especially by Sternberg and by Warthin) to the fact that in ordinary non-chloromatous cases of lymphoid leukemia, the hemopoietic tissues occasionally invade and infiltrate organs not precisely as sarcoma

does, yet in a manner suggesting it. Sternberg accordingly proposes the term "leukosarcoma" for such cases. Starting in the thymus, the tonsil, the sternum, the intestine, or elsewhere, the growths penetrate and destroy neighboring tissues, yet preserve all the while a structure indistinguishable from that of the glands and marrow of lymphoid leukemia.

Warthin[1] reported a case in which a process essentially identical with lymphoid leukemia (as we ordinarily recognize it in the marrow, spleen, and lymph glands) appeared to originate in the lymphatic tissue about the intestine and mesentery, which (with the stomach) were infiltrated almost from end to end with a growth composed of cells of the "large lymphocyte" type. There were metastases in the lungs, liver, kidneys, and marrow. The process also involved diffusely the spleen and marrow, but the changes were much less marked there than in the intestine. In the peripheral lymph glands no changes were found. There was no considerable anemia, although normoblasts and megaloblasts were fairly abundant. The blood showed 97 per cent. of mononuclear, non-granular cells, most of which are described as very atypical lymphocytes.

It is obvious from the cases above mentioned, as well as from others of a similar nature, that *the leukemic process can start wherever in the body leukoblastic tissue is present, that it may penetrate and invade other tissues,* breaking through the bones (as in chloroma), through the glandular capsules, and through the limits ordinarily preserved by the gastro-intestinal lymphatic tissue. It can give rise to "metastases," although it is doubted by some authorities whether these "metastases" are due to cells transported by the blood or lymph. If the "stimulus" which started the parent growth is exerted also upon some of the innumerable minute foci of leukoblastic tissue scattered through every organ and tissue of the body, foci indistinguishable from "metastases" may arise. It is notable, however, that the leukemic (or leukoblastic) infiltrations and metastases do not give rise to the ordinary amount of reaction in the tissues which they invade. Shall we say that we are dealing with malignant tumors in cases like the above? If so, shall we say that all leukemia is neoplastic? I think we must conclude that *there are transitions from ordinary sarcoma through Sternberg's leukosarcoma and through myeloma to leukemia of the ordinary type.*

4. **Leukemic Blood without Leukemic Changes in the Blood-making Organs.**—(*a*) One of the most remarkable cases of this type is that reported by Simon.[2] Following a crush of the leg with multiple fractures, the patient's blood was found to present the picture of myeloid leukemia. With recovery of the leg the blood became and remained normal. (*b*) Symptomatic leukemia in ordinary sarcoma (cutaneous, glandular, etc.) with normal bone-marrow has been reported. (*c*) The enormous circulating lymphocytosis of whooping cough and tonsillar adenitis may render the blood indistinguishable from that of lymphatic leukemia.

5. **Cases Presenting a Group of Changes which More or Less Recall Leukemia.**—(**Stimulation Myelocytosis**).—(*a*) In various infectious diseases (diphtheria, empyema, scarlet fever) we find sometimes a moderate degree

[1] *Transactions of the Association of American Physicians*, 1904, p. 421.
[2] *Am. Jour. Med. Sc.*, 1906, vol. 132, p. 444.

of myeloid change in the marrow or in the lymph glands, with relatively small numbers of neutrophilic myelocytes in the blood. Nothing properly called leukemia here exists, either in the blood or blood-making organs, but both suggest it. (*b*) In v. Jaksch's disease ("anemia infantum pseudoleukemia") we have a collection of various atypical cases of secondary anemia, pernicious anemia, (perhaps) splenic anemia, and pseudoleukemia, having in common certain points of resemblance to leukemia, viz., enlarged spleen, circulating myelocytes, nucleated red cells, and anemia with some increase of leukocytes.

Pseudoleukemia.—A group of German writers[1] attempted to work out a new concept of pseudoleukemia as a disease to be distinguished both from Hodgkin's disease and from the conglomerate of various infectious granulomata (tuberculosis, syphilis, etc.). They distinguish pseudoleukemia as a hyperplasia of specifically hemopoietic tissue closely akin to leukemia; in fact, distinguished therefrom solely by the absence of "leukemic" changes in the peripheral blood. This latter distinction is, however, one of degree, and intermediate forms with slightly or moderately leukemic blood ("sub-leukemia") are recognized. The disease may affect the hemopoietic system as a whole or in any of its parts (spleen, marrow, or glands), and accordingly medullary, splenic medullary, glandular, and other combined forms are recognized. The number of cases corresponding to these types is small but steadily growing.

Pappenheim regards the disease as sometimes a "forme fruste," sometimes an early stage of ordinary leukemia, and (in its medullary forms) a transition stage between glandular or splenic pseudoleukemia (with anemia) and true leukemia. The picture is admittedly indistinguishable from the condition of an ordinary case of *leukemia in remission* (whether due to infectious complications, *x*-ray treatment, or unknown causes). Obviously some of the cases reported as "leukemia" are practically identical with the condition here described, and it must also be added (to our confusion) that in some cases of pernicious anemia the postmortem findings are remarkably like those of "medullary pseudoleukemia with myelophthisic anemia" (Pappenheim). *The blood* may be (*a*) altogether normal, or (*b*) qualitatively but not quantitatively leukemic. Without necropsy diagnosis is obviously impossible, for the characteristic changes in blood-making organs are essential. In symptoms, course, prognosis, and treatment the disease is identical with leukemia.

Chloroma.[2]**—Definition.**—An atypical form of leukemia in which green tinted leukoblastic marrow-growths penetrate their bony shell, especially the skull bones, and invade the surrounding tissue.

Conditions of Occurrence.—Up to 1904 there were but 36 cases more or less fully recorded (Dock[3]). As in other types of leukemia males predominate (29 to 9), but the average age (eighteen years) is considerably younger than in the other forms.

[1] Pappenheim, *v.* Baumgarten, Sternberg, Benda, and others (see Folia *Hæmatologia*, 1906, p. 453 et seq., and Sternberg, loc. cit).

[2] Tück, *Ein System de Lymphomatosen.* Klein and Sternhaus, *Zentralb, f. path. Anat.*, 1904, p. 49. Sternberg, *Path. der Primarerkrankungen des Lymph. u. Hematopoet. Apparat. Wiesbaden*, 1904, p. 156.

[3] *Transactions of the Association of American Physicians*, 1904, p. 64.

Symptoms and Signs.—1. *The pressure of the tumors produces:* (*a*) exophthalmos, 11 cases; (*b*) deafness, 10 cases; (*c*) swellings in the temporal region, 8 cases; (*d*) blindness, 4 cases; and (*e*) pain, which, especially in the head or legs, is very constant.

2. *Constitutional* (*toxic?*) *manifestations* are early and marked: (*a*) Anemia in 11 cases, (*b*) early weakness in 9 cases, (*c*) hemorrhages in 8 cases, and (*d*) emaciation in 6 cases.

3. *Visceral infiltrations* are manifested during life in: (*a*) splenic enlargement, 7 cases; (*b*) hepatic enlargement, 3 cases; and (*c*) glandular enlargement (cervical, 11 cases; other glands, 8 cases).

Pathology.—Infiltrating tumors are found frequently in the orbit (12), the dura (9), temporal bone (7), temporal fossa (8), the vertebræ (10), the ribs (8), and the sternum (7); also in the kidneys (12), the liver (8), the marrow (7), the spleen and intestine (each 3), the skin (3), and in many other situations. With such a multiplicity of points of attack, it is obvious that the various combinations of pressure symptoms, perversions of organic function, and constitutional manifestations make the symptoms too protean and too variable for any brief description.

The Blood.—In almost all the well-studied cases the blood has shown the characteristics described in the section on acute lymphoid leukemia. In at least 2 cases, and possibly in 1 other, the blood has been that of myeloid leukemia. We must therefore recognize myeloid as well as lymphoid forms of chloroma.

The *course of the disease* is short, five and one-half months being the average duration under observation and eighteen months the longest known case.

LEUKANEMIA.

This is a term coined by Leube,[1] in 1902, and since retained because it recalls and pictures the confusion which the study of a group of cases has produced in hematological theory and terminology. The dilemma is this: Cases occur in which the blood picture is partly that of leukemia and partly that of pernicious anemia, while the postmortem findings are also more or less equivocal. To these cases Leube gives the name "*leukanemia,*" moved thereto by the following observation: A boy, aged ten years, succumbed after but two weeks' illness to an intense anemia (red cells 256,000 per cmm., color index 2, megaloblasts predominating over normoblasts). The leukocyte formula strongly suggested acute myeloid leukemia (leukocytes, 10,600; neutrophilic myelocytes, 13 to 15 per cent.; eosinophiles, 0.8 per cent.; small lymphocytes, 22 to 35 per cent.; polynuclears, 44 to 53 per cent.). The spleen, liver, and bone-marrow presented essentially the appearances of ordinary myeloid leukemia. There were no deposits of iron.

Since 1902 about a dozen cases have been published under the title of leukanemia, and both before and since 1902 a number of other and very similar cases have been published under different names, such as "atypical leukemia" (Herschfeld[2]), "splenomegaly with anemia and myelemia"

[1] *Deutsch. Klinik.*, 1902, Nr. 42.
[2] *Folio Hæmat.*, 1904, No. 3.

(Weil and Clerc[1]), aplastic leukemia (pseudoleukemia). All the cases fall into three groups: 1. Those identical with pernicious anemia in most respects, but showing some minor deviations. 2. Those identical with leukemia in most respects, but showing some minor deviations. 3. Those in which the traits of leukemia and of pernicious anemia are so evenly balanced that they present a genuine difficulty in diagnosis.

Before examining in detail the reported cases, certain of the known facts about leukemia and pernicious anemia should be recalled.

Facts about Leukemia.—1. That toward the end of most cases of leukemia the supervention of an intense anemia, with few, many, or most of the marks of pernicious anemia, is the rule and not the exception. We should not think of saying merely on this account that most leukemic cases become "leukanemic" before death.

2. That toward the end of some cases of leukemia with complicating infections the number of white cells falls nearly or quite nearly to normal, while the already existing anemia becomes intensified.

3. If one chanced to see a case of ordinary leukemia for the first time after (*a*) the supervention of the terminal anemia, or (*b*) the terminal fall in the leukocyte count, one would be in the presence of most of the evidence on which the diagnosis of "leukanemia" is usually based. Yet such a diagnosis would seem quite unnecessary to one who had watched the patient in the previous non-anemic, typically leukemic stage.

4. "Acute" cases of leukemia, both of the lymphoid and (less often) of the myeloid type, are not uncommon. Many of those are practically identical with some of the cases printed under the title "Leukanemia."

Facts about Pernicious Anemia.—Approaching next from the other side of the difficulty, we note: 1. That in the blood of most patients with pernicious anemia there is present sooner or later a small percentage of myelocytes. In the writer's series these were cases showing 0.5 per cent., 2 per cent., 3.5 per cent., 5 per cent., 7 per cent., and 10 per cent.

2. That in the marrow, sometimes also in the spleen, of cases of pernicious anemia we often find a proportion of myelocytes larger than in health.

3. That a marked terminal lymphocytosis has been repeatedly found in patients who for years had run the course and shown the blood typical of pernicious anemia.

4. Finally, we must remember that in children any influence which stimulates any part of the marrow to activity (*e. g.*, infection, anemia, toxic states, leukemia) is prone to rouse the *whole* marrow in greater or lesser degree. Thus infectious leukocytosis in infancy is often accompanied by a "shower" of nucleated red cells, and any type of anemia is apt to be accompanied by leukocytosis, enlarged spleen, and even myelemia. Hence leukemia or pernicious anemia in children or young people is especially likely to approach that apparent fusion of the two diseases which is suggested in the word "leukanemia."

Bearing in mind, then: (1) How much there is and has long been in the classic picture of leukemia to remind us of pernicious anemia. (2) How

[1] *Soc. de Biol.*, June, 1904.

much there is in the classic picture of pernicious anemia to remind us of leukemia. (3) How prone is the child's hemopoietic system to give a general response to a special stimulus—to function as a whole with less of differentiation and specialization that we expect in the adult—we may conclude that *with very few exceptions the cases reported as leukanemia can be put back into the old categories.*

Most of the cases reported under the title "Leukanemia" seem to the writer to be *leukemia*, more or less atypical, but still leukemia. In this group belong the cases of Hirschfeld,[1] Drysdale, Kormoczi, Kerschensteiner, Luce, and Mattirolo. The cases reported by Leube, Weber, and Bushnell and Herter may be classed as pernicious anemia. Until some more definite criteria are furnished whereby we can distinguish the cases of "leukanemia" from the leukemias with terminal anemia and from the pernicious anemias with lymphoid or myeloid marrow, there seems no reason why the term leukanemia should be adopted, and we may hope that (like the anemia infantum pseudoleukemia) it may be allowed to perish by disuse.

POLYCYTHEMIA (ERYTHROCYTOSIS MEGALOSPLENICA).[2]

In 1892 Rendu and Widal called attention to a new symptom-complex in which they noted (1) chronic cyanosis due to polycythemia, and (2) splenic enlargement. The condition was attributed by them to primary *splenic tuberculosis.* Vaquez, in 1899, Tück, in 1902, and Osler, in 1903, brought the syndrome into general notice, showed that there was no reason to attribute it to splenic tuberculosis, and gave grounds for believing that the disease is due to a primary hyperplasia of the erythroblast bone-marrow. Since that time many other reports have been published, so that there are now at least 50 cases on record.

Age and Sex.—The cases are about equally distributed in both sexes, and occur, as a rule, between the thirty-fifth and the sixtieth year.

Symptoms.—The patients seek advice, as a rule, on account of (1) the abnormal color and condition of the skin and mucuous membranes; (2) the symptoms of cerebral congestion (headache, vertigo, etc.); and (3) weakness. The facial color is a peculiar, mottled, brick-red, with a purplish tint in the lips and ears (a "red Indian," one of the patients was called), but on the unpractised eye the *cyanosis* of the lips, nails, and many other parts makes the strongest impression. Browish pigmentation may occur. The tongue and buccal mucous membranes are of a deep purple, and hemorrhagic oozing from the gums is a frequent result of the intense congestion and malnutrition.

[1] The literature of "leukanemia" is summarized in the articles by Hirschfeld, *Folia Hæmatologia*, 1906, p. 332; by Drysdale, *Quarterly Journal of Medicine*, October, 1907, and by Kerschensteiner, *Münch, med. Woch.*, 1905, Nr. 21.

[2] Englebach and Brown, *Jour. Am. Med. Assn., October* 20, 1906 (contains an excellent bibliography of the references up to that date). Watson, *Liverpool Medico-Chir. Journal*, July 19, 1906. Köster, *Niiond med. Woch.*, 1906, liii, 23. Senator, *Zeit. f. klin. Med.*, vol. lx, p. 357. Hirschfeld, *Therap. de Gegen.*, vol. xlvii. Nr. 8. Weber, *Lancet*, November 24, 1906. Aldrich and Crummer, *Jour. Am. Med. Assn*, April 6, 1907.

Other evidence of peripheral congestion is found in: (*a*) *Hemorrhage* from the nose, stomach, bowel, lung, skin, and genital tract. (*b*) *Cerebral Disturbances.* Besides headache and vertigo, which are the commonest and mildest, we have occasionally cerebral hemorrhage (hemiplegia, monoplegia, facial paralysis), paraphasia, muscular spasms, and other paroxysmal attacks. (*c*) *Facial neuralgia* (also erythromelalgia in 2 cases). (*d*) *Dyspnœa* and *œdema of the lungs.*

Gastro-intestinal symptoms, circulatory, respiratory, and genital symptoms (except as above noted), are not prominent. The urine is often normal, or shows a low specific gravity with or without polyuria, a trace of albumin and hyaline and granular casts in moderate numbers. Urobilin is sometimes present. The fundus oculi is deep red; the veins are enlarged, purple, and very tortuous. The temperature, pulse, and respirations are usually normal.

Physical Examination.—Besides the points above noted, the most important are (*a*) splenic enlargement, and (*b*) the blood findings. The *spleen* was demonstrably enlarged in at least 85 per cent. of the cases so far reported. It may fill half of the abdomen, but is usually of moderate size, reaching to or nearly to the level of the navel. The shape of the organ and its notches are preserved. The surface is smooth and hard. Pain, tenderness, and dragging sensations in the splenic region are often complained of.

The Blood.—Viscosity is markedly increased. The *red cells* are usually above 8,000,000 at some period of the disease, and in about one-half of the cases counts of 10,000,000 to 13,000,000 are recorded. The *hemoglobin* is from 120 to 200 per cent. (19 to 26 grams). The *leukocytes* are also increased, as a rule. About half the cases show over 20,000 leukocytes per cmm. at some period. Still more constant is the increase in the relative (and absolute) number of polynuclear neutrophiles, which in two-thirds of the cases ranged from 75 to 92 per cent., with a proportionate decrease in the percentages of lymphocytes. In Weber's case and a few others there was leukopenia.

Other *evidences of abnormal marrow activity* are seen in the presence of normoblasts, which are noted in most of the cases in which a careful search for them was made, of megaloblasts (numerous in Aldrich and Crummer's case), and of myelocytes. In the case just mentioned there were 6600 erythroblasts per cmm., a majority of them of the megaloblastic type, and 211 myelocytes (4.5 per cent.) per cmm. The large mononuclear (marrow?) lymphocytes are also increased (11 to 24 per cent.) in most cases. The red cells occasionally show variations in size, shape, and staining reaction. The blood plates are usually increased. *Enlargement of the liver* has been noted in the majority of cases, but it is decidedly less striking than the splenomegaly. *The muscular and mental weakness* is constant and usually progressive. There are not infrequently attacks of sudden prostration, faintness, or giddiness, as in Ménière's disease.

Pathology and Pathogenesis.—The number of autopsies is still small. Splenic tuberculosis was present in the earliest French cases, but not in most of those later reported. Its etiological significance is dubious. Widal believes that by the loss of functioning splenic tissue the activities of

the marrow are abnormally stimulated, so that hyperplasia and polycythemia resulted. Vivid purple marrow, with erythroblastic and leukoblastic hyperplasia, is the most constant anatomical finding. In the femur of Watson's case the compact bone was slightly encroached upon and the shaft was abnormally brittle. Rosengart found also evidence of erythroblastic and leukoblastic metaplasia in the spleen and liver of one case. On the other hand, "normal marrow" (microscopically) is reported in Saundby and Russel's case, and Watson found only intense vascularity and congestion in the spleen. Rechzeh considers blood stagnation from diminished venous tonicity as the cause of the disease, but his reasons do not seem convincing.

Diagnosis.—The commoner causes of cyanosis—cardiac and pulmonary disease, local pressure or paralysis, methemoglobinemia and other intoxications, etc.—must be excluded. This done, the presence of marked polycythemia with enlarged spleen is sufficient, although not absolutely certain evidence of the presence of the disease. The existence of tuberculosis in the spleen or elsewhere in the body does not negative the diagnosis of primary polycythemia.

Prognosis.—Recovery has not yet been reported, but in some cases the disease lasts for many years; six to eight years is the average, although one of Tück's patients died in three months.

Treatment.—Bleeding gives marked although temporary relief. Splenectomy has been several times performed, but not with results that justify us in advising the operation, especially as the not infrequent hemorrhagic tendency in the disease increases the already considerable operative risk. Herschfeld advises the iodides. *X*-ray treatment has given on the whole the best results. The size of the spleen and the blood count may be considerably reduced and the patient's condition improved. The technique is similar to that advised in myeloid leukemia.

CHAPTER XVII.

PURPURA AND HEMOPHILIA.

By JOSEPH H. PRATT, M.D.

PURPURA.[1]

Purpura is the name applied to spontaneous hemorrhages developing in and beneath the skin and mucous membranes. It is a symptom seen in a variety of pathological conditions. In idiopathic or primary purpura, spots of cutaneous hemorrhage constitute the chief symptom, the cause of which is at present unknown. Thus the term purpura is used to indicate both a symptom and a disease. The disease purpura or *morbus maculosus* may be defined as a condition characterized by an acquired hemorrhagic tendency, usually transitory, which manifests itself by hemorrhages into the skin or from the mucous membranes, or both combined.

Classification.—Our ignorance of the true nature of the purpuras is shown in the widely varying views held in regard to their proper classification. Some writers deny the existence of purpura as an essential disease, and refuse to admit that cases developing without apparent cause and presenting symptoms in common should be regarded as a clinical entity. They look upon it solely as a cutaneous eruption accompanying a number of morbid states. This view was advanced as long ago as 1874 by Mollière,[2] and was held by Stephen Mackenzie. Hoffmann, Litten, and most other German writers embrace all the primary purpuras under the denomination "Morbus maculosus Werlhofii," of which purpura simplex is the mildest and purpura hemorrhagica the gravest type.

Those who regard purpura as only a *symptom* are obliged to admit that in many cases the purpura is primary with no associated condition or cause to which it might be attributed. In 200 cases of purpura analyzed by S. Mackenzie,[3] and arranged as regards probable cause, no less than 68 were tabulated as "unexplained." If to these be added the cases with arthritis, 71 in number, it will be seen that 70 per cent. of his cases of "symptomatic purpura" might be classed as idiopathic or primary purpuras. It is highly probable that the morbus maculosus of the Germans includes several distinct disorders. It is possible, however, that purpura simplex and purpura fulminans simply represent a mild and severe form of the same affection. In purpura simplex a few small spots of hemorrhage on the legs may be the only sign of disease, while purpura fulminans

[1] The writer was aided in the preparation of this article by material placed at his disposal by Sir. William Osler, consisting of the notes of many private cases, unpublished lectures, and abstracts of articles in the literature. The statistical data are based largely on the clinical records of the Massachusetts General and the Johns Hopkins Hospitals.

[2] *Ann. de Dermat.*, 1873–1874, vol. v, pp. 44, 104.

[3] *Allbutt's System of Medicine*, 1898, vol. v, pp. 568–585.

usually runs its course and ends in death within twenty-four or forty-eight hours.

It is true that purpura is the name of a symptom, but this is not sufficient reason for refusing to apply this term to idiopathic cases in which cutaneous hemorrhage is the primary and dominating feature in the disease-picture. Anemia is a symptom and not a disease, yet cases of severe progressive anemia developing without any discoverable cause are properly grouped under the term primary pernicious anemia.

Secondary Purpura.—Purpura in Acute Infectious Diseases.—It may occur during the course of any infectious disease, and in typhus fever the eruption is usually purpuric. It is not uncommon in smallpox and cerebrospinal meningitis; in fact, purpura is more frequent in smallpox than in any other of the acute exanthemata. It is seen particularly in the early stages of the disease before the characteristic eruption appears. In ulcerative endocarditis the occurrence of purpura is so common as to be of diagnostic value. The hemorrhagic variety of scarlet fever and measles is rare, but less so than that of typhoid fever. Purpura may result from vaccination.

Purpura in Chronic Disturbances of Nutrition.—Cases of this type are often described under the heading of *cachectic* purpura. Purpura may develop in Bright's disease, heart disease, pernicious anemia, general disturbances of nutrition, cancer, Hodgkin's disease, leukemia, tuberculosis, icterus gravis, chronic alcoholism, and other conditions. In pernicious anemia the writer has seen an extensive extravasation of blood into the subcutaneous tissues of the thigh, producing induration of almost stony hardness (scorbutic scleroderma), which extended from Poupart's ligament to near the level of the knee. Severe purpura hemorrhagica has been repeatedly observed in lymphatic leukemia.

The occurrence of the hemorrhagic diathesis in chronic nephritis deserves special consideration. The table prepared by S. Mackenzie from the records of the London Hospital showed in that institution that purpura occurred more frequently in nephritis than in any other chronic disease. Analysis of our series of cases brought to light the same fact. Riesman[1] reported 2 cases, both ending fatally. Purpura cannot be considered as a common complication of nephritis, and Bamberger observed only 5 cases among 2340 cases of renal disease. It should be remembered that all forms of purpura are rare.

Bensaude et Rivet[2] claim that chronic purpura is not uncommon in tuberculosis. Among their 36 cases of chronic purpura hemorrhagica, 7 occurred in tuberculous subjects, while in 5 more tuberculosis probably existed.

L. Brown states that among 1000 cases of pulmonary tuberculosis at the Adirondack Cottage Sanitarium there were 3 cases of purpura hemorrhagica. Cruice[3] reported 8 cases of purpura among 1626 ward patients at the Phipps Institute. Only 1 of these was purpura hemorrhagica.

Senile Purpura.—The term purpura senilis was given by Bateman, who was the first to recognize the condition. "It appears principally along

[1] *Am. Jour. Med. Sci.*, 1907, cxxxiv, 709.
[2] *Presse méd.*, 1906, xiv, 469.
[3] *Am. Jour. Med. Sci.*, 1912, cxliv, 875.

the outside of the forearm, in successive dark-purple blotches, of an irregular form and various magnitude" (Bateman[1]). To the same type of eruption the name purpura cachectica has also been given. The backs of the hands and the forearms are more frequently involved than in any other form of purpura. The purpuric patches are usually of larger size than in the other forms of symptomatic purpura; it is doubtful if this form is as common as statements in the text-books indicate, and Bateman saw only a few cases.

Toxic Purpura.—Iodine heads the long list of drugs that may under exceptional conditions produce purpura. The iodides do not give rise to purpura except in individuals with marked idiosyncrasy. It is of very rare occurrence considering the extensive use of the iodides in medicine. Not a single case of iodic purpura was found in the records of the Out-Patient Department of the Massachusetts General Hospital among 96,600 patients treated there in four years. All forms of drug purpura are rare. Only three cases were seen at the London Hospital in a period of sixteen and a half years.

Grossman[2] reported a case in which epistaxis occurred after iodine had been taken for five days and petechiæ appeared two days later. After the purpura disappeared half a gram of potassium iodide was given one morning, and on the evening of the same day a new crop of purpuric spots developed. Although usually a benign affection, grave symptoms may arise, and death has occurred. S. Mackenzie recorded a case in which fatal purpura resulted from a single dose of 2.5 grains of potassium iodide in an infant five months old.

A remarkable case of iodic purpura was seen in the Boston City Hospital. The fingers were swollen and covered by large hemorrhagic blebs, while on the tip of the nose was a black necrotic area 2 cm. in size. Over the thighs was a typical purpuric eruption with spots 0.5 to 1 cm. in diameter. The patient had been given 180 grains of potassium iodide during a space of four days. At the end of that time the purpura and the blebs on the fingers developed. Among Osler's clinical records is an instance of acute febrile purpura due to iodine. In this patient there was an extensive urticarial rash associated with purpuric spots. It is said that the lesions in drug purpuras show a greater tendency to become gangrenous than in purpura induced by other causes. These 2 cases of iodic purpura are the only instances of so-called toxic purpura in the present series. E. Wagner says that *mercury* stands next to iodine in the frequency with which purpura follows its use. He states that mercury given as an inunction is more liable to cause purpura than when administered internally. He was obliged to abandon that form of mercurial treatment several times owing to hemorrhages from the nose and mouth as well as into the skin. Bateman refers to a case of mercuric purpura which resulted in death. Rudaux[3] reported a fatal instance of purpura hemorrhagica apparently caused by a single large dose of antipyrine. Other drugs said to produce purpura are chloral hydrate, copaiba, quinine, belladonna, arsenic, turpentine, phena-

[1] *Practical Synopsis of Cutaneous Diseases*, third edition, London, 1814.
[2] *Rev. prat. d. mal. cutan.*, 1906, v, 231.
[3] *Comptes rendus de la Soc. d'Obstét., de Gyn. et de Péd. de Paris*, October, 1903, v.

cetin, ergot, and salicylic acid. Snake venom produces hemorrhagic extravasations with great rapidity.

Nervous Purpura.—There are well-authenticated instances of purpura developing after severe fright in individuals of nervous temperament. Probably neuropathic influences are concerned in the production of the purpuras characterized by periodic recurrence. A case was observed at the Massachusetts General Hospital. The patient, a woman aged twenty-eight years, in place of the menstrual flow had an attack of vomiting every three weeks for a period of more than a year. For five months previous the vomiting had been accompanied by a copious purpuric eruption on the arms, legs, and trunk. The vomitus never contained blood. On examination purpuric spots were found on the parts mentioned. Some of the hemorrhages were about 4 cm. in size. She was seen eighteen months later in a similar attack. Cazenave observed a periodical monthly purpura in a young girl who had never menstruated. Apert[1] reported a case in a man who had hemorrhages from the rectum recurring regularly every month for six years. Except during the first two years, each attack was accompanied by a crop of purpura. In a case described by Trousseau, an eruption of purpura urticans accompanied each menstruation for a year or more. Purpura occurring during pregnancy (Brieger) and childbirth probably does not belong in this group.

Weir Mitchell reported 3 cases characterized by severe neuralgia and muscular spasms in which purpuric spots appeared at or near the painful points. Bouchard has observed purpura in trifacial neuralgia, and Faisans in sciatica. Purpura has been described in connection with the lightning pains of tabes (Straus), in hemiplegia on the paralyzed side (Gilbert), and in multiple sclerosis (Chevalier).

Mechanical Purpura.—The hemorrhagic spots that may appear after an epileptic seizure or a paroxysm of whooping-cough are of this type. Numerous petechiæ are sometimes produced on the knee by the application of a tight bandage around the lower portion of the thigh. Bramwell regards the purpuric eruptions which develop on the dropsical lower extremities in the terminal stages of cardiac disease as frequently mechanical in origin.

The fact that the eruption in every form of purpura is almost always more abundant on the legs than elsewhere is probably the result of mechanical influences. Attempts to sit up after an attack of purpura may be followed by the appearance of a new crop on the legs. *Purpura orthostatique* is the name given by Archard and Grenet[2] to this condition. A striking example of this type was under observation at the Massachusetts General Hospital in a woman aged twenty-four years. Three weeks prior to her entrance she had been suddenly seized with pain and swelling in both feet. A large crop of purpuric spots covered the feet and lower legs. She stated that since the onset new blotches appeared, accompanied by swelling of the feet and severe pain, whenever she attempted to sit up or walk. The day after admission the spots had almost entirely disappeared, so she was placed in a chair with her feet bandaged, but the feet swelled as before and a purpuric rash developed on the heels, which were uncov-

[1] *Bull. méd.*, 1899, xiii, p. 9.
[2] *Soc. méd. des hôpitaux*, January 29, 1914.

ered by the bandage. Three days later another attempt was made after flannel bandages had been applied to the feet and legs as high as the knees. Purpuric spots appeared on both thighs and on the ankles below the malleoli. One day a fresh crop was produced by moving her to a sofa. For five weeks she was obliged to remain in bed. As long as she was at rest in the recumbent posture no new spots developed. In this case the influence of mechanical factors is clearly shown, yet they were not the primary cause of the condition, for the tendency to hemorrhage was transitory. Hence it belongs in the group of essential or primary purpuras.

Idiopathic Purpura.—Frequency of Occurrence.—Only when other diseases and toxic conditions have been excluded is the diagnosis of primary purpura justifiable. At the Massachusetts General Hospital 65 cases of idiopathic purpura occurred among 155,884 medical and surgical in-patients during thirty-three years. At the Johns Hopkins Hospital 41 cases were observed in 18,594 medical patients. At the Hamburg General Hospital there were 73 cases in forty-one years in a total of 100,000 patients (Scheby-Buch). Thirteen cases occurred in the Mary Magdalene Hospital of St. Petersburg during twenty-four years, among 82,000 patients (Masing). S. Mackenzie states that of 63,834 cases in the London Hospital there were 200 cases of purpura. This included symptomatic as well as idiopathic purpura. In the experience of some physicians the disease is more common than these figures indicate. Thus, Bramwell[1] observed 16 cases among 5256 ward patients in the Edinburgh Royal Infirmary, and in 7686 private patients 9 were cases of purpura.

Table of 258 Cases of Primary and Secondary Purpura.

	Cases.
Primary Purpura: Simple purpura	45
Simple purpura with arthritis	54
Purpura hemorrhagica	52
Henoch's purpura	43
	194
Secondary Purpura: Typhoid fever	10
Nephritis	8
Tuberculosis	7
Heart disease	6
Lymphatic leukemia	5
Ulcerative endocarditis	4
Rheumatism	4
Hepatic cirrhosis	3
Jaundice	3
Iodic purpura	2
Carcinoma of gall-bladder	1
Tumor of the liver	1
Alcoholic neuritis	1
Nervous purpura	1
Whitlow	1
Pneumonia	1
Arteriosclerosis	1
Chorea	1
Chronic arthritis	1
Pernicious anemia	1
Marasmus	1
Aneurism	1
	64

[1] *Clinical Studies*, 1905, iii, p. 325.

Etiology.—Sex and Age.—Laache states that purpura simplex and purpura rheumatica occur more frequently in the male sex, especially near the time of puberty. Women are said to be more predisposed to purpura hemorrhagica than men. The disease is most common in the second decade, 48 (25 per cent.) of this series developing during this period. Among 90,556 sick children Gross found 41 cases. The disease purpura is rare after fifty years of age. In this series 129 of the patients were males and 65 females; 27 of the cases of purpura simplex were in males and 14 in females. Purpura rheumatica was more common in males; there were 38 cases in males and 16 in females. Purpura hemorrhagica occurred 30 times in males and 20 in females.

Seasonal Frequency.—It is asserted that the disease occurs more frequently in the fall and winter, and is more prevalent some years than others. The series of 194 idiopathic cases observed in Boston and Baltimore offers no support for either of these claims. The Massachusetts General Hospital records analyzed for this purpose cover a period of thirty-four years, and the Johns Hopkins Hospital records eighteen years.

There is no evidence that damp dwellings or a delicate constitution exert any particular influence in the production of purpura. Of course, lowered vitality and poor hygienic surroundings would favor the development of disease. Strong, well-nourished individuals are sometimes struck down with purpura hemorrhagica while apparently in perfect health.

Heredity.—Förster observed the disease in three sisters. Bauer speaks of a number of families in which several of the members at a certain age suffered from purpura. Dohrn reported a case in which purpura was transmitted from a mother to her newborn child. Cousin[1] reported 3 cases in different branches of one family.

Pathogenesis.—In its production the bloodvessels are certainly concerned, but the changes in them may be secondary to alterations in the blood. Probably a generalized vascular injury plays an essential part in the production of purpura but the nature of the changes in the vessels is unknown. The hemorrhages into the skin are frequently associated with œdema, erythema and urticaria, and all these lesions are the expression of pathological alterations in the vessels. Some circulating poison damages the cells of the capillary wall and the exudate results. The angioneurotic type of purpura is possibly an anaphylactic phenomenon. Certainly the symptoms of serum sickness reproduce in a striking way the features of an angioneurosis. In purpura hemorrhagica the blood platelets are greatly reduced, but in other forms of purpura they are present in normal number.

The view that purpura is an *infection* has had many advocates. Streptococci and staphylococci have been repeatedly found in the secondary purpuras of septicemia. In idiopathic purpura, however, blood cultures have been repeatedly made by recent investigators with negative results.

The vascular alterations that have been observed at autopsy are not constant, and seem to throw little light on the cause of idiopathic purpura. Whether the erythrocytes leave the vessels by rhexis or diapedesis is not

[1] *Ann. de méd. et chir. inf.*, October, 1913, vol. xvii.

known. Many pathologists have examined purpuric spots without finding any breaks in the vascular walls. Clinicians have objected to the theory of primary vascular degeneration as a cause of typical purpura hemorrhagica, for the reason that the hemorrhages are widely distributed over the surface of the body and often develop with great rapidity. Such a generalized and speedy alteration of the vessels has seemed improbable. Furthermore, the tendency to hemorrhage is transitory. Hence it is difficult to reconcile the clinical picture of a severe, rapidly developing disease of short duration with a serious disease in the vessels. If purpura is due to endarteritis and hyaline degeneration of the vessels, one would expect that the hemorrhages would continue indefinitely. It is possible, however, that the vascular injury may consist of a fatty metamorphosis, which is frequently of short duration and may be followed in the heart and liver by complete restoration of structure and function. Flexner discovered a substance in snake-venom possessing the property of destroying endothelium, and to which he gave the name hemorrhagin. The injection of snake-venom into laboratory animals is followed in a few minutes by multiple hemorrhages. The hemorrhagins contained in different venoms are not identical. Gay and Southard found in their study of anaphylaxis that hemorrhages occur with extraordinary rapidity, and focal fatty changes with hemorrhage are observed in as short a time as four minutes. They assert that at least a part of the hemorrhages in their experiments were due to endothelial changes in the capillaries. These studies are certainly suggestive that in purpura there may be some substance in the blood that produces an endotheliolysis with focal hemorrhages.

Changes in the Blood.—Considerable evidence can be adduced in favor of the view that at least one type of purpura, namely purpura hemorrhagica, is due to a pathological condition of the blood.

The Blood Platelets in Purpura Hemorrhagica.—A reduction of the platelets in purpura hemorrhagica was first observed by Denys, a Belgian histologist, in 1887. He later reported three cases in which platelets were almost absent in fresh blood films. The first platelet count in a case of purpura hemorrhagica was made by Hayem in 1890 who found the number reduced to 69,000 per cmm. The normal number of platelets as determined by Hayem's method was 250,000. Additional cases were studied by Hayem and Bensuade and a reduction of the platelets was found to be a characteristic feature of purpura hemorrhagica. Hayem's lowest count was 42,000. Helber, using a new counting method, found 40,000 platelets per cmm. in one case of purpura hemorrhagica. The methods of counting platelets employed by Hayem and Helber yield too low results, in fact the error amounts to nearly 50 per cent. The writer has devised a method which gives much more accurate results by which the average number of platelets in health is 469,000, which is nearly twice that obtained by the methods of Hayem, Helber, or Wright and Kinnicutt. In the first edition of this work a case of severe purpura hemorrhagica was reported in which the platelet count dropped to 7000. That was the lowest platelet count recorded up to that time. Selling[1] has since reported

[1] *Bull. Johns Hopkins Hospital*, 1910, xxi, 33.

a fatal case of purpura hemorrhagica complicating benzol poisoning in which a count of only 2500 platelets was obtained with my method, and Duke,[1] a remarkable case with 6000 one day, none the next, and 3000 the third day. The platelets are greatly reduced in chronic as well as in acute purpura hemorrhagica. I saw with J. W. Coe, a patient with chronic purpura hemorrhagica in whom the platelet count was 29,000 per cmm. and in another case it was reduced to 22,000. Coe[2] reported five cases of hemorrhagic diathesis, in all of which the one constant feature was the great reduction in the blood platelets.

In one of my cases it was noticed that a sudden drop in the platelet count preceded a severe hemorrhage. From a careful study of the blood in purpura hemorrhagica, Coe was led to the conclusion that there is a close relationship between a greatly diminished number of platelets and the liability to hemorrhage. Coe's observations have been confirmed and extended by Duke[3] who found the platelet count was always very low when the hemorrhages were severe. He studied 8 cases of purpura hemorrhagica and observed a marked reduction of the platelets in every instance. In two cases he at first thought that all the platelets had disappeared as none could be found in stained films or in the counting chamber when Wright's procedure was used, but in both cases the presence of a few platelets was demonstrated in the undiluted plasma by Bürker's method. A rise in the platelet count was always associated by marked lessening of the bleeding. In one of Duke's cases the platelets increased from a number so small that they could not be counted by the method he employed to more than 100,000 in twenty-four hours. The bleeding-time which had been much delayed became normal and the hemorrhages which had been severe entirely ceased within the same short space of time.

Purpura hemorrhagica is not the only condition in which the blood platelets are greatly diminished. In lymphatic leukemia a low count is the rule. In pernicious anemia the number is reduced, but in less degree. In both these conditions severe purpura is a well-recognized complication. Gley[4] found that injections of albumose into the circulation of animals diminished the number of platelets. Krehl and the writer made a similar observation. Duke was able to reduce greatly the platelet count in rabbits and dogs by subcutaneous injections of benzol, diphtheria toxin, and tuberculin. In one rabbit which had received diphtheria toxin the platelets suddenly fell to 4000 nine days after the last injection. The following day petechiæ appeared on the ears.

In hemophilia and in the hemorrhagic form of scorbutus there is no reduction in the number of platelets.

Method of Counting Platelets.—The ratio of platelets to red blood corpuscles having been obtained in fresh preparations and a count of the red blood corpuscles having been made in a Thoma-Zeiss apparatus, the number of platelets per cmm. is easily calculated. For counting the platelets the blood is mixed with the following preserving fluid: Sodium metaphosphate (Merck), 2 grams; sodium chloride, 0.9 gram; distilled water, 100 cc. The slides and cover-slips are cleaned in strong sulphuric acid

[1] *Jour. Am. Med. Assn.*, 1910, lv, 1185.
[2] *Ibid.*, 1906, xlvii, 1090.
[3] *Arch. Int. Med.*, 1912, x, 445.
[4] *Soc. de biol.*, December 19, 1896.

saturated with potassium bichromate. A large-sized platinum loop of the pattern used in bacteriological work is filled with preserving fluid and the centre of the loop is brought in contact with a drop of blood obtained immediately after pricking the ear. The diluted blood is then transferred to the slide and without delay the cover slip is placed over it. There should be three or more parts of fluid to one of blood. An oil immersion lens and an Ehrlich's ocular are used in making the counts. A satisfactory substitute for Ehrlich's ocular is made by placing a diaphragm cut out of cardboard in an ordinary ocular. Two preparations are made, and in each the platelet and erythrocyte count should be continued until the total number of erythrocytes reaches 250 or 500. Additional details of the technique are given elsewhere.[1]

Retraction of the Clot.—Hayem has described another remarkable alteration of the blood in purpura hemorrhagica. Normally a blood clot quickly retracts from the sides of the vessel in which it is contained and expresses serum. The clot in purpura hemorrhagica does not retract, and there is no extrusion of serum. The test is performed as follows: About 3 cc. of blood are collected in a small test-tube. Normally the surface of the clot becomes concave in about fifteen minutes. At the end of an hour it begins to be separated from the wall of the test-tube. At the end of twenty-four to forty-eight hours the retraction should be complete and the clot entirely surrounded by a layer of serum. Occasionally it remains fastened to one side of the wall. In the first case of purpura in which Hayem found the platelets greatly reduced in number, the blood clotted in five minutes. At the end of twenty-four hours, however, there was no retraction of the clot and no extrusion of serum. In other cases similar observations were made. According to Hayem the pathognomonic characteristics of true purpura hemorrhagica are the rarity of the blood platelets and the absence of expression of serum after coagulation of the blood. Hayem's observations on the non-retractility of the clot have been confirmed by Millard, Apert, Lenoble, and Duke. Hayem reports a case in which a *crise hematoblastique* (sudden diminution in the number of platelets) coincided with sudden development of this modification in coagulation.

Failure of retraction occasionally occurs in symptomatic purpura. This alteration was observed by Hayem in a tuberculous subject without hemorrhage from the mucous membranes. There were very few platelets in the blood and the clot did not transude any serum. He says that the absence of retraction is seen in certain infectious states without any diminution in the number of platelets. According to Hayem's view, substances exist in certain toxemias whose presence gives rise to an abnormal fibrin that has lost its property of contraction. Apert and also Allacia found no diminution of platelets and normal retraction of the clot. Retractility is favored by the addition of liver extract to the blood (Gilbert and Weil).

Le Sourd and Pagniez,[2] state that this phenomenon—failure of the clot to retract—has been repeatedly observed when the number of blood plate-

[1] *Jour. Am. Med. Assn.*, December 30, 1905.
[2] *Jour. de phys. et path. gén.*, July 15, 1907, lx, 154.

lets is increased. Nevertheless, on the basis of the experimental work, they attribute retraction of the clot to the blood platelets. They found that clots formed by the coagulation of oxalate plasma, rennin plasma, and hydrocele fluid do not retract. If one adds blood platelets to them they produce clots that do retract, and the degree of retractility varies with the number of platelets added. This property of the blood platelets is thermolabile. It is impaired by heating to 45° to 50° and destroyed at 58° C. A serum that destroys blood platelets can be obtained by injecting blood platelets from rabbits into guinea-pigs. Such a serum checks the retraction of the clot. If this serum is introduced into the circulation of the living animal, it reduces the number of blood platelets and renders the blood clot less retractile.

The Coagulation Time in Purpura.—In the majority of cases the blood coagulates within the normal time. The blood of patients with purpura hemorrhagica gave a retractile clot upon the addition of a suspension of blood paltelets.[1] In this series there are 34 cases of idiopathic purpura in which the coagulability of the blood was determined. These observations were made in the Johns Hopkins and Massachusetts General Hospitals. The average time in this series was five and a half minutes. Brodie and Russell's method was the one chiefly employed. Hinman and Sladen,[2] in a careful study, have shown that with the Brodie-Russell method records below seven to eight minutes are normal. In several instances in our series the clotting was retarded, in one case to fourteen and a half minutes, and in another thirteen minutes, but no direct connection could be traced between delayed coagulation and the severity of the hemorrhagic tendency. The hemorrhagic diathesis in cholemia differs in this respect from that in idiopathic purpura; thus in a case of obstructive jaundice with hemorrhages the coagulation time was found by the writer to be over one hour by the Brodie-Russell method. Hinman and Sladen observed greater retardation of the coagulation time in malignant jaundice than in any other condition.

These studies of the coagulation time would indicate that there is no marked deficiency in the fibrin factors in purpura and Howell[3] found no variation from the normal in either prothrombin or antithrombin.

Bleeding Time.—This is a measure of the tendency to bleed from fresh cuts devised by Duke. Blot up on absorbent paper all the blood which flows from a small incision of the ear at intervals of thirty seconds. Each drop will then give the volume of blood shed in its respective half minute. The duration of such a hemorrhage is called the bleeding time. The normal bleeding time is one to three minutes. When the blood stops in from five to ten minutes it is considered slightly prolonged. This is sometimes seen in severe anemia. In purpura hemorrhagica of the type associated with a reduced platelet count Duke found the bleeding time greatly prolonged, ranging from twenty minutes to several hours. When the hemorrhages cease the bleeding time at once drops to normal. The decrease in size of the drops on the absorbent paper is a trustworthy index

[1] *Bull. et Mém. Soc. méd. d. hôp. de Paris*, July 12, 1912.
[2] *Bull. Johns Hopkins Hosp.*, 1907, xviii, 207.
[3] *Arch Int. Med.*, 1914, xiii, 76.

of the bleeding time. When the twentieth drop is half the size of the first the bleeding time is moderately prolonged, if it is as large as the first the bleeding time is enormously prolonged. Duke found the bleeding time normal in purpura simplex, purpura rheumatica, Henoch's purpura, and scurvy.

Changes in the Nervous System.—A type of symptomatic purpura occurring in association with diseases of the nervous system has been described. Several cases of purpura have been reported in which there has been a segmental distribution of the purpuric outbreak similar to that in zona.[1] Unfortunately the condition of the ganglia of the posterior roots in none of these cases has been ascertained. Pressure from a surgical dressing near the elbow has been followed by a purpuric eruption sharply limited to the area supplied by certain cutaneous nerves (Gougerot and Salin[2]). Grenet observed a case in which a crop of herpetic vesicles on the face succeeded the purpuric rash. The symmetrical distribution of the eruption so often seen in purpura is regarded as an indication of some relation between the nervous system and the cutaneous outbreak. Lumbar puncture has sometimes shown a distinct meningeal reaction. Lymphocytosis may be marked and considerable albumin present. Two of Grenet's 4 positive cases were in tuberculous subjects. Some observers have reported negative results after lumbar puncture. *Cerebral hemorrhage* is one of the serious complications of purpura.

Bacteriological Studies.—It was held long ago by certain writers that purpura hemorrhagica was an infectious disease, and a dozen or more investigators have announced that they found bacteria in the blood. Recent investigators, working with improved methods, have obtained negative results. Blood cultures were made from several patients of the present series but no microörganisms were obtained. Litten excised during life bits of skin covered with petechiæ, but could find no microorganisms. Streptococci and *Staphylococcus pyogenes aureus* have been isolated from the blood in cases of symptomatic purpura due to sepsis. Le Count and Batty have described a remarkable case apparently due to a paratyphoid bacillus.

Pathology.—In cases in which death results from hemorrhage the anemia of the viscera is the most striking and constant finding at autopsy. Petechiæ and ecchymoses in the peritoneum, pleura, pericardium, and endocardium are common. Hemorrhage into the bone-marrow has been reported (Ponfick). Cerebral hemorrhage has been repeatedly observed and was the cause of death in four cases of this series. Wagner reported a number of cases in which there were hemorrhages into the brain and its membranes similar to those in the skin. In one instance pachymeningitis and a fresh effusion of blood were found. The bleeding is sometimes subdural or subpial. In 5 of Wagner's fatal cases there were numerous fresh hemorrhages in the brain itself. Hemorrhage into the subcutaneous tissues and into the muscles is more apt to occur in purpura hemorrhagica than in other forms of purpura (Heubner).

[1] Armand-Delille, *Rev. neurol.*, 1905, xiii, p. 775.
[2] *Arch. des Maladies du Cœur*, 1911, iv, 86.

Bleeding into the joints in purpura, if it ever occurs, must be excessively rare. Hoffmann says he could not find a definite instance of hemorrhage into a joint in morbus maculosus. Wagner searched the literature up to 1886 without finding a single case of purpura in which a large hemorrhage had occurred into a serous sac—a condition not uncommon in scurvy. No case has been found in the recent literature.

There is a record of only one case of purpura rheumatica that came to autopsy, which was reported by Leuthold from Traube's clinic. There was an œdematous swelling of the capsule of the affected joint and injection of the synovial membrane, with an increase in synovial fluid, which was slightly turbid. The appearance of the joint was said to be quite like that seen in rheumatic fever and in gonorrhœal arthritis.

Small hemorrhages in the mucous membrane of the stomach are very common, but whether they bear any relation to hemorrhage from the stomach is doubtful. Extensive bleeding into the walls of the stomach or intestine is rare. Thatcher reported a case in which there was extensive necrosis of the stomach wall that resulted in a large perforation. In one case at the Boston City Hospital the wall of nearly the entire small intestine was infiltrated with blood and serum. The diffuse hemorrhage was below the mucosa, and there was no blood in the lumen of the gut. The kidneys are the chief source of blood in hematuria, which is a common symptom of purpura hemorrhagica. The pathological histology of the type of nephritis that so frequently develops during purpura has been studied in but few instances. In one case examined by W. G. MacCallum the kidneys were greatly enlarged, measuring each 12 x 7 cm. There was extensive degeneration in the renal epithelium, but changes in the glomeruli formed the most striking feature. The Malpighian tufts were compressed, by crescentic masses of cells, in the capsular spaces. There was not only a proliferation of the epithelial cells but also a new-growth of connective tissue in the capsules (adhesive glomerulonephritis). In a case of acute nephritis, which terminated with symptoms of the hemorrhagic diathesis, the capsular form of glomerulonephritis was found by the writer. Hemorrhage into the adrenals may occur. Wolff, in a case of only fifteen hours' duration, found the adrenals greatly enlarged, owing to a diffuse hemorrhagic infiltration. Litten observed a case in which there was an adrenal infarct the size of an apple.

All pathologists have agreed with Willan that hemorrhages from the lungs are rare in purpura. They were present in two of this series. In one there was a hemorrhagic infiltration of a lobe and clotted blood in the bronchus; in the other the lungs were studded with hemorrhages. Bleeding into the globe of the eye, producing total blindness, occurred in one case of the present series, and Pepper has reported two cases in which complete destruction of vision in one eye has resulted. Small ulcers may develop on the skin, lips, or mucous membrane of the mouth. Gangrene has been observed. In one case sloughing of the anterior two-thirds of the tongue occurred (Fayrer). Musser observed in two instances sloughing of the uvula, and Prentiss gangrene of a portion of the anterior abdominal wall, which was the seat of hemorrhage. Recovery occurred in all of these cases of gangrene.

PLATE XIV

Purpura.

Symptoms.—Characteristics of the Eruption.—The hemorrhages in the skin usually vary in size from a pinhead to a split pea. Occasionally they are several centimeters in size. Rarely large areas of skin are embraced in a single hemorrhage, or through the confluence of several hemorrhages a considerable extent of surface is involved. The spots are sometimes oval, but usually round. Ring-shaped figures may form (see Plate XIV), but they are very rare. The large patches of hemorrhage often have an irregular contour, giving the skin the appearance of a map. The small spots of hemorrhage are known as *petechiæ*. Dominici[1] designates as petechiæ all purpuric spots less than 10 mm. in size. Lines or streaks of hemorrhage are *vibices*. Larger areas are called *ecchymoses*. The term *suggillation* is applied to an extensive ecchymosis. A fresh eruption is usually bright red but soon becomes livid or purple. The color does not disappear on pressure. Fading occurs within a few days. The colors change from bluish hues to brownish-yellow, as they do in ordinary "black and blue" spots resulting from trauma. In a week or so all trace of the eruption disappears, or only a yellowish stain remains. Finally the blood pigment is absorbed, not leaving a trace behind. Successive crops are common, and the spots, of different age and color, give the skin a variegated appearance. The purpuric eruption occurs chiefly on the extremities, particularly the legs, and is often more marked on the extensor surface. The distribution of the eruption in the present series of 194 cases of idiopathic purpura was as follows: legs, 162; arms, 86; body, 64; face, 28. Petechiæ may appear on the tongue, gums, or elsewhere in the mouth. In pure purpura the spots are not elevated about the surface and there is no induration of the underlying tissues. Gangrene is a rare termination. It occurred in only 2 cases in the present series of 258 cases of idiopathic and symptomatic purpura. Another rare complication is the formation of hemorrhagic or clear blebs (pemphigoid bullæ) on the surface of the hemorrhagic spots. According to Batēman, hemorrhagic vesicles are more common on the mucous membrane of the mouth than in the skin. Superficial ulceration of the purpuric spots has been described, and occurred in one of this series. The ulcer was painful and healed slowly. There is an intimate relation between purpura, urticaria, erythema, and angioneurotic œdema. This will be discussed under the clinical varieties of purpura.

The Blood.—There is apparently a close relationship between aplastic anemia and purpura hemorrhagica. The failure of regenerative processes in the bone-marrow is the essential feature in aplastic anemia, and the diminished number of platelets in purpura hemorrhagica probably indicates failure of some regenerative process in the bone-marrow, for the reason that aside from purpura hemorrhagica great reduction in the number of platelets is seen only in diseases involving the bone-marrow and in which the blood-making function is diminished or disturbed, namely, lymphatic leukemia and pernicious anemia. In mild cases of purpura there may be no demonstrable blood change.

The Color Index.—The fall in hemoglobin is often much greater than the reduction in red blood corpuscles; Musser and Litten have called

[1] *La pratique dermatologique*, Paris, 1904, iv, 158.

attention to this fact. In five of this series the color index was 0.6, and in one instance it was 0.3.

Leukocytosis.—There is often a slight increase in the number of leukocytes above the limit of normal. In two cases of Henoch's purpura the count was 30,000. The leukocyte counts in 59 cases of idiopathic purpura showed from between 3000 to 4000 in 2, 4000 to 5000 in 2, 5000 to 6000 in 2, 6000 to 8000 in 10, 8000 to 10,000 in 8, 10,000 to 12,000 in 13, 12,000 to 15,000 in 9, 15,000 to 20,000 in 6, 20,000 to 25,000 in 4, and 25,000 to 30,000 in 3.

Metabolism.—Magnus-Levy found serious disturbance of metabolism in a case of purpura hemorrhagica. There was evidence of rapid and extensive destruction of tissue, which he attributed to the loss of blood. In a case of Henoch's purpura studied by Edsall[1] a large amount of nitrogen was excreted in the urine. On two days when the patient, a lad sixteen years of age, was taking no food the nitrogen output was 22.5 grams and 23.7 grams. Five days later when there was a return of some symptoms but no hemorrhage the nitrogen in the urine was 22.6 grams. The phosphates were increased. The studies of Hawk and Gies show that hemorrhage alone does not lead to great tissue destruction.

Clinical Varieties and Symptomatology.—The old view that purpura simplex, purpura rheumatica, and purpura hemorrhagica are distinct diseases has been largely abandoned. It is necessary, nevertheless, for purposes of study and description to retain these clinical terms until additional knowledge of the nature of idiopathic purpura (morbus maculosus) is acquired. The several varieties exhibit different grades of intensity, but all are characterized by the special feature of hemorrhage either into the skin or from the mucous membranes, or both, but the small number of platelets in the blood in purpura hemorrhagica would indicate an essential difference in pathogenesis between this type and the other forms of purpura in which the platelets are not reduced.

Purpura Simplex.—A purpuric eruption in the skin is usually the only symptom. The purpuric spots are, as a rule, small and the eruption symmetrical on the legs and arms. The legs are the favorite location, but the arms are involved in a considerable number of cases. Spots on the face were noted in four instances in our series. The disease is generally afebrile. Slight fever was noted in only 2 instances among 34 cases of simple purpura. There may be slight pains in the muscles or joints. If the arthritic manifestations are at all marked, the case should be classed as purpura rheumatica, or, better, simple purpura with arthritis. Slight nausea and vomiting may usher in the attack, but the writer cannot agree with Graves that diarrhœa is common in this form of purpura; it occurred in only one case of this series. In 3 cases albumin was present in the urine. Although common in children, in our experience more cases occurred during the fourth decade than at any other period. The duration is stated in text-books to be from one to two weeks, but in our experience it is much longer, the average duration being six weeks, excluding the chronic cases more than one year's duration. The eruption comes out in crops. Simple

[1] *Am. Jour. Med. Sci.*, 1905, cxxx, 589.

purpura of the chronic type is a well-recognized condition. The duration in 5 of this series was from one to three years. Hayem observed a patient in whom recurring attacks persisted for more than ten years.

Purpura Rheumatica.—This is a bad term for what is nothing more than simple purpura with arthritic manifestations. A still worse designation, because even more misleading, is *Peliosis rheumatica* of Schönlein. Arthritis occurs frequently in association with idiopathic purpura, as was discovered by Johann Schönlein. It is strange that such acute observers as Willan and Bateman overlooked entirely the relation between purpura and arthritis.

The name peliosis rheumatica is doubly objectionable, because it is not a distinct disease, as the word peliosis implies, and the condition is probably not related to rheumatism. It is important to understand how great was the confusion introduced into the clinical conception and classification of the different varieties of purpura by Schönlein's description of peliosis rheumatica. Exactly what he embraced under this name is unknown. All the knowledge we have of his views is contained in the notes of his lectures published anonymously "by some of his students." Pagel[1] says that this work was unauthorized and that the notes give a very inaccurate presentation of Schönlein's teaching. In this description the definite statement is made that the spots "*bei'm Drucke des Fingers verschwindend.*" If this be correct, and Schönlein referred to a condition characterized by spots that disappear on pressure, then peliosis rheumatica is not a purpura but an erythema. Traube, who was closely associated with Schönlein for a period of nineteen years, first as student, later as assistant and colleague, must have been familiar with what the latter diagnosed as peliosis. From Traube's clinic a fatal case of purpura with arthritis was reported under the name of peliosis rheumatica. This would indicate that Schönlein employed this term to designate a purpura rather than an erythema. The following are the characteristic features of peliosis given in the original description: The patients have either previously suffered from rheumatism or at the time of the attack rheumatic pains develop in the joints, particularly the knees and the hands, which become swollen and tender. The erythematous spots appear in the majority of cases, first on the extremities, usually the legs, and only as high as the knees. The spots are small, varying from the size of a lentil to a millet seed, and not raised above the surface. At first bright red, they become dirty brown, then yellowish. There is some desquamation. Repeated outbreaks of the eruption occur often for several weeks, and fever is usually present. The disease differs from morbus maculosus of Werlhof by the absence of hemorrhage, the character of the eruption, the small size of the spots, which never become confluent, blue, or livid, the joint affection, and the lack of nervous symptoms. It is evident that Schönlein described to his students with clearness and exactness the disease picture as he had seen it, but, as Litten points out, it is also evident to anyone who has seen many cases of purpura or who is familiar with the literature of the subject, that Schönlein's clinical experience with the dis-

[1] Article on Schönlein in *Hirsch's Biographisches Lexikon*, 1887, v, 269.

ease was too limited to give any value to this definite clinical picture that he drew. It was later shown by Scheby-Buch that arthritis might occur in purpura hemorrhagica, *i. e.*, purpura associated with bleeding from the mucous membranes, as well as in purpura unaccompanied by free hemorrhage.

If the term Schönlein's purpura is to be used at all, it should be employed to designate the group of symptoms described. Even during Schönlein's lifetime the term peliosis rheumatica had ceased to have any definite meaning and had become a stumbling-block in the path of progress. The conception of what constituted the disease underwent various modifications. Fuchs and Hebra said the eruption extended over the entire body. They stated that the joint-symptoms occurred only as prodromal symptoms. Bohm maintained that they occurred later in the disease. The vagueness was increased by the publication from Frerich's clinic of a case of ulcerative endocarditis in which hemorrhages from the skin and mucous membranes, as well as the arthritis, were attributed to peliosis rheumatica. In 1860 Bamberger published a monograph on nephritis, in which he wrote these words: "The so-called peliosis rheumatica involving the lower extremities is not uncommon in Bright's disease." He then referred in detail to two cases of secondary purpura in nephritis. Instead of applying Schönlein's name to a definite form of hemorrhage—characterized by petechiæ varying in size from a millet seed to a lentil, never confluent, located chiefly on the legs, rarely extending above the knee—it has been employed, as Litten says, to designate every form of cutaneous hemorrhage associated with joint symptoms, including scurvy and erythema nodosum.

The text-books of today give descriptions of Schönlein's peliosis rheumatica that vary widely from one another. Strümpell says that in peliosis rheumatica hemorrhages from mucous surfaces sometimes occur. In other words, he would group under this heading any case of purpura associated with arthritis. Osler states that Schönlein's disease "is characterized by multiple arthritis and an eruption which varies greatly in character, sometimes purpuric, more commonly associated with urticaria, or with erythema exudativum." He says that the diagnosis is not difficult, as the association of multiple arthritis with purpura and urticaria is very characteristic.

Under the term *simple purpura with arthritis* (purpura rheumatica) are grouped all the cases of purpura with arthritic manifestations uncomplicated with hemorrhage from any mucous membrane. In the series of 194 cases of idiopathic purpura, 54 cases fell into this class. This division is convenient for purposes of description, yet doubtless quite artificial, as arthritis of the same type is seen in purpura hemorrhagica and in Henoch's purpura. Simple purpura with arthritis occurs chiefly between the ages of ten and fifty. It is most often seen in young adults, and is more common in males than in females. A previous history of rheumatism was noted in only 5 cases of this series. The average duration of the entire illness was five weeks, although cases of two weeks' duration were not infrequent. The arthritic symptoms usually persist only a few days, but they frequently recur. As a rule, several joints are affected and the knees

and ankles are most commonly involved. There may be swelling or tenderness or pains in the joints, or the three symptoms combined. The swelling is usually slight, and the tenderness and pain are rarely as marked as in typical cases of acute articular rheumatism. The pain may shift from joint to joint. The arthritic symptoms are frequently the first manifestation of the disease, and may be indistinguishable from those seen in rheumatic fever. Within a day or two the purpuric outbreak generally occurs, and with its appearance the arthritic symptoms often subside. Sometimes the joint symptoms and the purpura develop simultaneously. The joint trouble may occur not at onset, but during the course of the disease. It may be transient and be present but once during a long illness. No relation can be traced between the severity of the pain and the amount of swelling. Pain and tenderness may be marked in a joint that is not at all swollen.

The purpuric eruption is similar to that in simple purpura; it is chiefly composed of petechiæ, although patches 3 cm. in size, or even larger, do occur. Cases have been observed in which the eruption appeared chiefly on the affected joints. Heubner cited a case in which the elbows, shoulders, hips, and knees were successively involved. On every affected joint simultaneously with the onset of pain and swelling purpuric spots appeared, and with the disappearance of the joint symptoms they faded. Tonsillitis or pharyngitis may precede an attack of purpura arthritica, although in our experience this mode of onset is rare. There is often diffuse pain in the muscles of the arms and legs. The purpuric rash usually recurs several times, and each crop may be associated with pains in the joints. The outbreak may be attended with a sensation of fulness or burning of the extremities. Itching is rare, but may occur without urticaria. In one case in which the eruption recurred repeatedly a sensation of cold preceded each crop of purpura. This prodromal symptom was noted by Willan. There may be malaise at the onset, with slight nausea and loss of appetite. Puffiness of the hands or feet is not uncommon, and there may be great œdema without any evidence of nephritis. In one case of this series there was marked swelling of the legs without nephritis or heart disease. In another the face became so swollen that both eyes were closed; the right forearm and one leg were the seat of a brawny œdema, and the urine was free from albumin. Typical angioneurotic œdema occurred in some cases and purpura arthritica is often associated with urticaria. The combination was noted in nearly 20 per cent. of the series. Erythema is probably more common than statistics indicate, as it is frequently overlooked. It was present in 8 of the series. The usual form is erythema multiforme, although simple erythema or erythema nodosum may occur.

Fever was present in less than half of the cases, and was usually slight and of short duration, but in several instances the temperature rose to 102° and the fever continued for a week or more. In these instances it was generally of the remittent type. Albuminuria occurs less frequently in this condition than in purpura hemorrhagica. In not a single case in the series did acute endocarditis occur as a complication, and no case has been found reported in this country in which acute endocarditis developed

secondary to purpura rheumatica. Suppuration of the joints or ankylosis never results. Chronic nephritis is a rare sequel. There is only one fatal case of purpura rheumatica with autopsy on record.

Relation of Rheumatism to Purpura.—Many writers, chiefly English and French, have maintained that purpura rheumatica is a form of rheumatic fever. After examining all the evidence it is difficult to see how any one can maintain, in the face of demonstrable facts, that the arthritis of purpura is rheumatic in origin. The following facts indicate that the arthritis of purpura is not due to rheumatism:

1. Pains and swelling in the joints may occur in association with effusion of blood in other parts of the body. Among Sir William Osler's records there are notes of two cases, in one of which the arthritis was in connection with hemorrhage into a pancreatic cyst; in the other a protracted arthritis followed a fall on the back, with resulting hematuria from laceration of the kidney.

2. In arthritic purpura a history of a previous attack of rheumatism is rare. It was elicited in only 5 out of our 54 cases of purpura rheumatica. The joint symptoms are usually transient and the pain not severe. Fever is absent in one-half the cases, and when present is rarely high. Hyperpyrexia was not observed in any of this series, and in only one was there profuse sweating. Endocarditis did not occur in any of this series. The pain in purpura arthritica, unlike that in rheumatism, is rarely relieved by salicylates.

3. If the so-called purpura rheumatica is a manifestation of rheumatism, why does purpura occur so rarely in typical febrile cases of rheumatic fever? This question, which Scheby-Buch raised over thirty years ago, has never been satisfactorily answered. In a search of the literature he failed to find a single case of purpura in which the typical picture of rheumatic fever was present. In a study of the records of 4000 cases of rheumatic fever he found only a single case in which it seemed quite probable that purpura was associated with true rheumatism, but even this may have been tuberculous arthritis. Undoubtedly symptomatic purpura may occur in rheumatism as in all other infectious diseases, but it is rare. In the records of the Massachusetts General Hospital there were only 4 cases of purpura in which it seemed at all probable that the disease was rheumatic in origin. At the Johns Hopkins Hospital, for fifteen years ending in 1904, there were 330 cases of rheumatic fever (McCrae), and there was not a single case of purpura in this entire number.

Purpura and Urticaria.—This association is frequent. Urticaria may occur in all forms of purpura, but it is most frequently seen in simple purpura with arthritis (purpura rheumatica) and in Henoch's purpura. It was noted in 11 of the 54 cases of purpura rheumatica in this series, and doubtless occurred in a mild form in many more cases than were recorded. Osler, who has been much interested in the relation of urticaria to purpura, reported the presence of urticaria in 17 out of 29 cases of "the erythema group with visceral lesions." Four types of eruption are seen: (1) The purpuric spots may be slightly elevated (purpura papulosa). This is the simplest form of purpura urticaria. (2) Hemorrhage into definite urticarial wheals. (3) Simultaneous outbreak of purpura and urticaria.

Purpura urticans includes these three types. (4) A purpuric attack may be followed by an urticarial eruption, or the reverse may occur. Osler reported a case in which, after outbreaks of urticaria for years, the final symptoms were those of a severe purpura hemorrhagica.

Sometimes the combination of purpura and urticaria gives the skin a remarkable appearance, as in a patient aged sixteen years, who was convalescing from an attack of simple purpura. In the morning only fading petechiæ were present, but at 5 P.M., over both lower legs, but chiefly on the outer side of each, a great number of wheals 5 to 7 mm. in size were present, so thickly set as to present the appearance of a coarsely grained leather or a pebbled surface. The color of the elevations was reddish and did not disappear on pressure. The infiltration of the skin of the affected area was marked. Scattered between the wheals were many fresh, bright red petechiæ the size of a pin's head and not elevated above the surface. Above the knees were scattered wheals and petechiæ, but none elsewhere on the body. There was no itching. On the next day, at 1 P.M., there was no trace of urticaria or infiltration of the skin remaining, and the sites of the wheals were represented by rose-colored petechiæ. The patient was aware of this outbreak of purpura, and the pulse and temperature were uninfluenced. He had no joint pains or digestive disturbances.

In one case (see Plate XIV) purpura urticans of unusual type recurred repeatedly during a period of two years. Colorless, circular nodules first appeared and became hemorrhagic. The areas extended peripherally, forming larger and larger circles; the advancing border was always indurated.

In purpura urticans itching may occur, but it is usually absent. On the other hand, itching may accompany a purpuric outbreak when no urticarial lesions develop.

Between urticaria and typical erythema transition forms exist which in local and general manifestations offer diagnostic difficulties (Wagner). Under the term urticaria are embraced those cutaneous exudations characterized by rapidity in developing and disappearing and the absence of desquamation. Sometimes erythema nodules become so filled with blood that they resemble a hematoma of traumatic origin. This condition is sometimes designated as purpura urticans, or urticaria hemorrhagica.

Purpura and Erythema.—Thibierge and other French writers group under the erythemas both the purpuras and the urticarias. The exudative erythema, according to Wagner, includes at least three different forms: (1) urticaria; (2) erythema exudativum multiforme; (3) erythema nodosum. Most authors do not include urticaria. Osler regards purpura rheumatica as the hemorrhagic type of an exudative erythema, and he would place Henoch's purpura in the same group. He has clearly demonstrated the close affinity that exists between exudative erythema, Henoch's purpura, and angioneurotic œdema.[1] It is quite possible that within a year in an individual patient the diagnosis might be given of simple purpura, purpura arthritica, angioneurotic œdema, exudative erythema, and simple urticaria.

[1] *Jacobi's Festschrift*, New York, 1900, 459.

Osler places all these conditions together in what he terms the erythema group. He has studied a series of 29 cases in which there were polymorphous visceral lesions, of which the most prominent were crises of abdominal pain and hemorrhages. Henoch's purpura belongs in this class. In 22 of the 29 cases there was purpura, in 17 urticaria, and in 14 erythema. The name is not entirely satisfactory for this group. It is, in fact, somewhat misleading and confusing, as the pure type of erythema was present in only half the cases, both urticaria and purpura occurring more frequently than erythema.

E. Wagner[1] wrote a valuable monograph on purpura and erythema. In a space of nine years he saw 19 cases in which there was a combination of erythema and purpura associated with acute joint manifestations; 10 of the cases were mild and 9 severe. The character of the erythema varied, but the most common form was erythema nodosum. The nodules after a shorter or longer time usually became hemorrhagic, and sometimes small hemorrhagic vesicles formed. The gastro-intestinal complications which were such a striking feature in Osler's cases of combined erythema and purpura were almost lacking in Wagner's series.

Erythema and purpura have many features in common. Both are rare, both affect chiefly young individuals, and they may occur simultaneously in the same individual. Prodromata of both diseases are often the same—general malaise, gastro-intestinal symptoms, pain in the limbs, and fever. In both affections arthritis of the same type and hemorrhages from the mucous membranes occur, and in both severe crises of abdominal pain may be present.

The similarity of purpura rheumatica and erythema exudativum is well shown in the following case seen at the Naval Hospital in Chelsea: The patient complained of general muscular and joint pains, specially marked in the elbows, wrists, knees, and ankles. His temperature was then 100°. The fauces were very red. An erythematous eruption was present on both hands and feet. During the next two days the fever ranged from 101° to 102°. He had slight epistaxis, headache, nausea, vomiting, and sweating.

The urine contained a trace of albumin. Three days later the joint pains had disappeared; there was a fading erythematous rash on hands and feet, with no infiltration of the underlying tissues, and in the left upper eyelid an ecchymosis 1 to 2 cm. in size. There was no swelling of the joints and the urine was free from albumin. An interesting feature was the simultaneous outbreak of a marked eruption of erythema and one purpuric spot.

Endocarditis, rare in purpura, is common in erythema exudativum. In Lewin's collection of 126 cases endocarditis developed in 27. In 64 cases of his series arthritis existed.

The arthritis of erythema, like that of purpura, has frequently been regarded as rheumatic in origin, notwithstanding the great rarity of erythema in typical cases of rheumatic fever. Pye-Smith found only 2 cases of erythema among 400 of rheumatic fever. Lewin concluded after care-

[1] *Deutsch. Archiv f. klin. Med.*, 1886, xxxix, 431.

ful study that there was no evidence that there was any connection between erythema and rheumatism.

In this series of 194 cases of idiopathic purpura there were 20 with erythema. The tenderness so characteristic of erythema nodosum has been seen in purpura unassociated with any induration of the tissues.

Purpura and Angioneurotic Œdema.—In 49 of the 194 cases of idiopathic purpura œdema was present, and in 6 instances typical angioneurotic œdema occurred, and many of the other cases were probably of the same nature, as œdema was transitory and often localized on the hands and face. Osler attributes the colic of Henoch's purpura to localized œdema of the intestinal wall. Definite colic occurred in 34 of this series. The sudden swelling of the hands and feet so frequently seen in purpura is probably related to angioneurotic œdema. As Osler has pointed out, there is really no warrant for separating angioneurotic œdema and urticaria too sharply. In two cases angioneurotic œdema, purpura urticans, and ordinary purpura occurred together. Oppenheimer has seen angioneurotic œdema and urticaria develop simultaneously. The intimate relation of purpura and angioneurotic œdema is shown in the case of a man aged fifty-five years who, during six weeks had "about two dozen" attacks of purpura of the legs, associated with transitory localized œdema of the legs. The swelling of the legs was so great in the first attack that his trousers had to be cut in order to remove them. The œdema developed with great rapidity, red spots being first noticed, and within five or ten minutes the swelling began. The last attack was accompanied by severe pain in the epigastrium and vomiting. On examination there was no œdema, but both legs were nearly encircled above the ankles by a band of discrete and confluent spots of dingy brick-red color, which did not disappear on pressure.

The Angioneurotic Group.—All these closely allied conditions—Henoch's purpura, erythema, urticaria, and localized œdema—are probably manifestations of an angioneurosis, and it would be well to group them, at least tentatively, under this name. Localized vascular dilatation or exudation (serous or hemorrhagic) occurs in every case, and the claim of an angioneurotic origin has already been made for each member of the group. The elder Romberg, Barensprung, and particularly Lewin regarded erythema exudativum as an angioneurotic dermatosis, and this view is held by most writers.[1] The angioneurotic dermatoses are characterized by a marked disturbance of the vascular tonus, in addition to a more or less pronounced inflammatory condition of the skin. They are due to an abnormal tendency of the skin to react to slight and varied irritants with the production of inflammatory changes (dilatation of the vessels and exudation), which must be regarded as constituting a distinct disease. This sensitiveness of the skin and the abnormal reaction is the result of a general angioneurotic disturbance. These dermatoses must be distinguished from the simple cutaneous inflammations which result from the action of inflammatory irritants upon normal skin (Auspitz). They include urticaria as well as the erythemas, and may result from the action of different toxins on the nerve centres (Caspary).

[1] Caspary, *Deutsch. Klin.*, 1905, x, 83; Géronne, *Ztschr. f. klin. Med.*, 1906 lx, 383.

Osler[1] in 1888 advanced the theory that the entire group may depend upon some poison "which in varying doses in different constitutions excites in one urticaria, in a second peliosis rheumatica, and in a third, a fatal form of purpura." Klippel and Lhermette[2] voiced the same opinion when they asserted that no sharp barrier can be set up between certain forms of purpura and erythema exudativum multiforme. "It is a question of virulence of the infectious agent or variation in the resistance." Acute localized œdema is generally regarded as an angioneurosis, as the name angioneurotic œdema indicates, and the same is true of dermatographia and factitious urticaria. In Henoch's purpura the view is widely accepted that the abdominal colic is due to angioneurotic œdema of the intestine.

Henoch's Purpura or Purpura Abdominalis.—This form of purpura is characterized by recurrent attacks of purpura and crises of abdominal pain often accompanied by vomiting and diarrhœa. The stools and the vomitus may contain blood. Arthritis is present in the typical form of the disease, and nephritis is a serious and very common complication. The relation of Henoch's purpura to other members of the angioneurotic group has been discussed on a previous page. Osler has shown that similar abdominal manifestations occur in erythema and urticaria. Henoch first observed this type of purpura in 1868, and six years later published a report of 4 cases.[3] Abdominal pain and even severe colic had been occasionally noted in cases of purpura since the time of Willan, but Henoch was the first to study them with care and to show their connection with the hemorrhagic process. The gastro-intestinal disturbances had previously been attributed to splenitis or to congestion of the liver.

It is a disease of early life, as shown in this series: One to 10 years, 11; 10 to 20 years, 19; 20 to 30 years, 6; 30 to 40 years, 3; and 40 to 50 years, 4. The youngest patient was four years and the eldest forty-seven years of age. Cases in children three years old have been reported (Olliviers d'Angers, Handfield Jones). In one of this series typical attacks of colic with arthritis began at the age of two years, but the patient did not come under observation until five years later, when purpura was present. It may have occurred during previous attacks and have been overlooked by the parents. The disease is more common in males than in females. In a series of 40 cases collected from the literature by v. Dusch and Hoche,[4] 33 were in males and 7 in females. Of our 43 patients, 31 were males and 12 females.

General Features.—The onset varies. Sometimes there is headache, anorexia, and prostration, or the purpuric outbreak or abdominal colic ushers in an attack. The patients complain of severe pain in one or more joints, similar in character to that in other varieties of purpura. Fever is usually absent, and when it occurs it is generally slight and of short duration. The appearance of the purpuric spots is often unnoticed by the patients, especially when confined to the legs and unattended with any

[1] *New York Med. Jour.*, December 22, 1888.
[2] *Arch. gén. de méd.*, 1904, i, 257.
[3] *Berl. klin. Wchnschr.*, 1874, Nr. 51.
[4] *Pädiatrische Arbeiten. Henoch's Festschrift*, Berlin, 1890, 379.

subjective sensation, such as burning, tension of the skin, or itching. The arthritis often precedes the purpuric rash by a period of several days. Soon the abdominal symptoms appear and dominate the scene. The pain is colicky in character, often agonizing, and forms the most distressing feature of the attack. It does not yield readily to treatment, and sometimes continues for days. At the onset of pain the abdominal wall is usually rigid and contracted and there is diffuse tenderness. At first the bowels are constipated, and if they do not move for several days the mistaken diagnosis of acute intestinal obstruction may be made. Often the initial constipation is followed by diarrhœa. Vomiting frequently adds to the distress of the patient; the vomitus, which at first consists of food, is later admixed with bile, and sometimes with blood. The pulse is small and frequent. After a few days the gastro-intestinal symptoms cease, the purpuric spots fade, the arthritis disappears, and convalescence seems established. The duration of a single attack may not be more than one or two days. The symptoms rarely persist for more than a week. The average duration of the entire illness in our series was one month.

Rarely does the disease consist in a single attack, for in the vast majority, after an interval varying from a few days to weeks or months, another attack occurs. Couty reported a case in which the symptom complex recurred nineteen times, but four or five recurrences are the rule. In a patient observed at the Johns Hopkins Hospital there must have been over sixty attacks; for over a period of five years typical gastro-intestinal seizures occurred with intervals of less than a month. It is the composite picture of the disease that has been sketched above. The individual cases present many variations. Henoch realized this, for he points out in his text-book that "single rings in the chain of symptoms may be lacking."

The recurrence of erythema and urticaria in association with Henoch's purpura has already been considered. Urticaria was present in 13 cases (30 per cent.) and erythema in 6. Œdema developed in 15 cases. Puffiness of the backs of the hands and swelling of the feet are common. In several instances typical acute angioneurotic œdema occurred. Not only has Osler shown the morphological inconstancy of the skin lesions, but he has reported cases in which in some of the attacks agonizing colic occurred without any cutaneous eruption. In 39 of this series there were purpuric spots on the legs, in 22 on the arms, in 14 on the body, and in only 4 on the face. The patients frequently locate the pain in the region of the umbilicus, a fact which v. Dusch and Hoche comment upon. In a considerable number the pain is in the epigastrium or the lower abdomen. Henoch states that in his cases there was always tenderness in the upper part of the abdomen. In 36 of the 43 clinical records the definite statement was made that the pain was colicky in character. Sometimes it shifts from one part of the abdomen to another. Colic may be the only symptom; more frequently there is also vomiting or diarrhœa. In this series vomiting occurred 31 times and diarrhœa 12 times. The passage of blood in the stools is more frequent than vomiting of blood. The former symptom was present 15 times and the latter only 6 times. The abdomen is sometimes distended; in one patient distinct waves of peristalsis were seen. Arthritic pains were present in all but 5 of the 44 cases analyzed by v. Dusch and

Hoche, while among this series of 43 cases they were noted in 27 of the clinical records. The knees and ankles were the joints most frequently involved. Epistaxis is not uncommon, and occurred in 8 of this series, while bleeding of the gums was noted in three instances.

Fever was present in one-third of the cases, but a temperature above 101° is rare. The spleen was not often palpable in this series, but it has been found enlarged by other observers in quite a number of instances. There is usually a slight leukocytosis. Blood counts were made in 16 cases, and in 2 a leukocytosis of 30,000 was recorded, but usually the number of leukocytes is below 14,000.

The most serious complication is *acute nephritis*, and in no other variety of purpura is it as common, being present in no less than 20 of 43 cases. It was frequently of the acute hemorrhagic type. There is usually a considerable amount of albumin and numerous tube casts. Œdema may be absent in a case of intense nephritis (Osler). Hematuria occurred in 4 cases of this series, and it has been shown that in this disease the kidney is the usual source of the blood in the urine. One of the two fatal cases in this series resulted from nephritis. Cerebral hemorrhage, endocarditis, pericarditis, and pleuritis are rare complications. Intussusception occurred in one case (Sutherland).

The cause of the gastro-intestinal symptoms is unknown. Scheby-Buch thought the colic might be due to hemorrhages in the serosa of the intestine. This explanation did not satisfy himself, however, and he called attention to the rarity in other diseases of the association of colic with intestinal hemorrhage. In a case that occurred at the Boston City Hospital there was no colic, although the autopsy revealed extensive hemorrhage and serous exudation into the wall of the small intestine. Sutherland[1] has reported a case in which localized hemorrhage beneath the serosa and thickening of the wall of the bowel were found at operation. In many of this series severe colic occurred unaccompanied by bleeding from the stomach or bowels. As has been stated, similar abdominal manifestations may develop in other members of the angioneurotic group, and Osler[2] has reported a case of generalized telangiectasis with similar attacks of colic.

Osler thinks that the pain in the abdomen is associated with a localized urticarial swelling of the gastro-intestinal wall. In fact, this condition has actually been found at operation made during an attack of colic (F. B. Harrington[3]). The studies of Lennander[4] indicate that either serous or hemorrhagic infiltration of the wall of the stomach or intestine, if sufficient to produce stretching of the parietal (mesenteric) attachments, would produce colic.

The Surgical Importance of the Recognition of the Visceral Crises.— The literature shows that at least six patients have been subjected to an exploratory laparotomy during the past few years for this form of colic. Thousands of attacks of severe colic occurred among the cases of Henoch's

[1] *Brit. Jour. Child. Dis.*, 1904, i, 385.
[2] *Bull. Johns Hopkins Hosp.*, 1907, xviii, 401.
[3] *Boston Med. and Surg. Jour.*, March 30, 1905.
[4] *Jour. Am. Med. Assn.*, September 7, 1907.

disease that have been reported. With the exception of one case in which intussusception was found at autopsy, recovery from the colic has occurred in every instance. The import of this should be recognized by every surgeon. No one should operate on a child with abdominal colic until the diagnosis of Henoch's purpura has been excluded. For this purpose a full history should be taken with special reference to intestinal crises, arthritis and skin lesions, and a careful inspection of the skin for purpura or other angioneurotic manifestations.

Purpura Hemorrhagica.—Hemorrhage from the mucous membrane is the feature that distinguishes this type of the disease from purpura simplex. Most of the serious cases of purpura are embraced in this variety. The onset is usually abrupt, the initial symptoms often severe. In some instances the bleeding from the mucous membranes is slight. The cutaneous hemorrhages in purpura hemorrhagica are usually more extensive and the body and face are more frequently involved than in purpura simplex. Large ecchymoses may cover the limbs and trunk. The skin may look as if it had been spattered with a paint-brush. In some cases slight pressure on the skin produces an extravasation of blood. All authors are agreed that epistaxis is the most frequent form of hemorrhage in this disease. In this collection of 48 cases of purpura hemorrhagica, bleeding from the nose occurred in 24 (50 per cent.). The gums were the seat of hemorrhage in 20 cases, while in 7 cases the blood came from other parts of the mouth. In Wagner's experience hemorrhage from the urinary organs was more common than from the mouth. In this series hematuria was present only five times. Bleeding may occur from other places—intestines, stomach, uterus, and rarely the lungs. In this list the cases of Henoch's purpura have not been included, although classed by some writers as purpura hemorrhagica. The rarity of erythema and urticaria in the latter indicates a difference in two conditions. Furthermore, the blood platelets are present in normal number in Henoch's purpura while they are greatly reduced in purpura hemorrhagica.

The *duration* of purpura hemorrhagica is usually longer than purpura simplex or the so-called purpura rheumatica. A few of our cases lasted only one to two weeks, but the average duration was two months. There is a chronic form which may persist for many years. A case of this type referred to under chronic purpura lasted more than thirty-six years.

French writers separate the febrile and the afebrile cases. The latter are grouped under the heading purpura hemorrhagica of Werlhof, while the former are regarded as infectious in nature and are placed in a class by themselves. Some would even subdivide them into typhoid and septic types. Many of the cases of so-called infectious purpura are doubtless symptomatic purpura in which the primary disease, *e. g.*, ulcerative endocarditis, has been overlooked. *Fever* was present in 25 of our 48 cases, but was usually mild, the maximum temperature being 103°. According to Kernig, continuous subfebrile temperature (99.5° to 100°) is not uncommon. If hemorrhage is severe, collapse with subnormal temperature may be present. Sometimes the spleen is swollen. The liver may be enlarged and painful, but this is rare. Slight icterus is not infrequent, according to Laache and Litten, but was not observed in any of this series.

Arthritis is common, although, singularly enough, the association of joint symptoms with purpura hemorrhagica was not known until Scheby-Buch published his monograph in 1874. He showed that the same type of arthritis existed in purpura hemorrhagica as in purpura simplex. In his series there were 20 cases of purpura simplex without and 18 with arthritis; 9 cases of purpura hemorrhagica with and 26 without joint symptoms. Rheumatoid pains of the joints and muscles occurred in 16 of our 48 cases of purpura hemorrhagica. Œdema was present in no less than 10 cases, the feet and legs being most commonly affected, but sometimes the hands, arms, or face. Vomiting is common, but diarrhœa is rare. Acute nephritis is the most important complication, owing to its frequency and its severity, and is usually of the hemorrhagic type. It is not as common, however, in this variety of purpura as in Henoch's disease. Owing to the greater loss of blood, anemia is more marked than in the other purpuric conditions. Hematorachis and hematomyelia have been described, but are excessively rare complications. Swelling of the testicle with hemorrhage into its substance has been noted by Eichhorst.

Purpura Fulminans.—In this very rare variety ecchymoses extend with startling rapidity, and within a few hours an entire extremity or the greater part of the trunk may assume a blue or reddish-black color. This disease usually ends fatally in from eighteen to forty-eight hours, and no patient has recovered. Guelliot, in 1884, was the first to describe this condition, which was more carefully studied by Henoch,[1] who gave the name purpura fulminans. There is no hemorrhage from the mucous membranes, and hence it comes under the heading of simple purpura. There is a certain irony in applying the term simple purpura to a disease that is one of the most surely and rapidly fatal of which we have knowledge.

Stybr could find only 13 cases in the literature up to 1906. Risel,[2] in 1905, analyzed 12 cases, but he did not include 5 American cases. All the typical cases have been in children, and the youngest was in an infant aged two months (Stybr). Three occurred during convalescence from scarlet fever. Bacteriological examinations were negative except in one case reported by Borgen, in which streptococci were found in the blood. This and one reported by Litten, of rapidly fatal purpura associated with streptococcus septicemia, should be placed among the secondary purpuras. Heubner is possibly right when he classes this type of purpura with the septic diseases. Litten and Nehrkorn have reported cases similar to purpura fulminans, but with much bleeding from the mucous membranes.

The duration has been from ten hours to five days, and all undoubted cases have been fatal. Hemorrhagic bullæ formed on the skin in 2 cases. Grozs and Goerges have reported cases in which recovery occurred, but Risel thinks they were dealing with erythema exudativum multiforme. Death from cerebral hemorrhage occurring in the beginning of an attack of purpura may lead to the mistake of diagnosing the case one of purpura fulminans. From a study of the literature it is apparent that some observers have fallen into this error.

The only case in this series exhibiting a fulminating character was

[1] *Berl. klin. Wchnschr.*, 1887, p. 8.
[2] *Ztschr. f. klin. Med.*, 1906, lviii, 163.

doubtless an example of some general infection.[1] The patient was a vigorous young man aged twenty-one years, who on December 21 was in his usual health. In the evening he carried a heavy trunk down stairs, and about 11 o'clock that night he began to feel sick and vomited. The next morning he complained of severe backache and his temperature was 102°. During the forenoon a purpuric eruption appeared on the face, and he died at 3.30 P.M. The entire duration of the illness was less than seventeen hours. Dr. Councilman made the autopsy. The face was thickly covered with purple spots and blotches, ring-shaped, varying in size from a pinhead to a bean. Similar spots were present over the shoulders and trunk, and in less number on the arms and legs. There were hemorrhagic spots in the subcutaneous tissues and on various serous membranes. There was acute congestion and œdema of the lungs. Cultures made from the kidney and lungs showed streptococcus and staphylococcus aureus in considerable number. The most extraordinary feature was revealed on the histological examination. Careful search failed to reveal a single normal polynuclear leukocyte in the tissues. Only a few polynuclear leukocytes were seen, and these were degenerated and their nuclei fragmented.

Chronic Purpura.—There are two forms of chronic purpura. In one the hemorrhages into the skin or from the mucous membranes continue uninterruptedly for years, while the other type is characterized by recurrent attacks separated by intervals of health. Wagner held that the disease occurred chiefly in childhood among the weak and anemic. He cites the case of a child aged five years who, every three or four days, during a period of three years, would be attacked by fresh hemorrhages; sometime petechiæ or large ecchymoses would appear, and sometimes there would be vomiting of bloody mucus or the passage of urine or feces mixed with blood. The patient recovered entirely. It is interesting to note that a paternal uncle died of acute purpura hemorrhagica.

Bensaude and Rivet[2] state that the *continuous* form of chronic purpura is the rarer. Subjects of this disease usually consult a physician on account of weakness or for some gastro-intestinal disturbance. On examination purpuric spots are found. In these individuals epistaxis and bleeding from the gums are common, but severe hemorrhages are rarely observed.

In the *intermittent* form the recurrence is usually preceded by frequent hemorrhage from a single mucous membrane, especially from the nose or mouth. The duration of this affection is variable. Attacks are said to have occurred over a period of more than twenty years. Bensaude and Rivet have observed 14 cases of chronic purpura hemorrhagica and collected 20 others from the literature. In one of their cases there was an interval of seven years between the second and third attacks. Mistakes in diagnosis have been common; when the hemorrhage has occurred from a single organ it has frequently been mistaken for a local disease. When the hemorrhages are multiple or follow slight trauma, this condition is frequently confused with hemophilia. In chronic purpura hemor-

[1] Dr. J. H. McCollom has seen an exactly similar case in a house epidemic of scarlet fever. He suggested to the writer the possibility that this was a case of scarlet fever.

[2] *Arch. gén. de méd.*, 1905, i, 193, 272.

hagica, the coagulation time is normal, but the clot remains absolutely non-contractile. The platelets are diminished. Bensaude and Rivet believe that the presence of these two characteristics of the blood will permit the diagnosis of chronic purpura even in the absence of a purpuric eruption. The prognosis in chronic purpura should be made with reserve. In view of the long latent periods, it is impossible to assert in any case that the disease has been cured. The mortality is high, according to Bensaude and Rivet; five of their patients died during attacks.

In this series are 20 cases of purpura in which the disease persisted for a year or more. This list includes simple purpuras with and without arthritis, purpura hemorrhagica, and Henoch's disease. The longest duration was thirty-six years. The patient had frequent recurring epistaxis with occasional crops of purpura since her tenth year. Only one of our chronic purpuras resulted fatally. Death in this case was due to cerebral hemorrhage. In 1898, Dr. Halsted operated on a woman for carcinoma of the breast who had had recurring attacks of purpura almost from childhood. There was no special bleeding at operation, and she made a good recovery.

Some cases of chronic purpura show a marked tendency to hemorrhage, as in a patient seen with J. W. Coe[1] in New York. He was at that time seventeen years old and had had recurrent attacks of severe epistaxis for twelve years, often accompanied by a purpuric eruption. At the age of thirteen, after having a tooth pulled, he bled profusely for three hours. The family history was negative. Examination of the blood showed the platelets to be greatly diminished in number, with the coagulation time normal.

Purpura Hemorrhagica without Skin Symptoms.—There are some cases of the hemorrhagic diathesis which present the clinical picture of purpura hemorrhagica, except that cutaneous hemorrhages are absent. There is no hereditary or congenital tendency to hemorrhage, and hence they are not hemophilia. In some chronic cases of this type the diagnosis is confirmed subsequently by the appearance of purpuric spots in the skin. Osler[2] has reported such a case with recurring abdominal crises and bleeding at the nose for a year, before a purpuric rash appeared during an attack. Bulloch and Fildes have shown that many cases have been reported as hemophilia that should be classed as purpura. A large proportion of these cases probably belong in the group under discussion.

J. W. Coe studied a patient in whom, during a period of twenty-eight years, there had been frequent attacks of epistaxis so severe that packing of the nostrils was often necessary. There was no history of bleeders in the family, and he had never had arthritis. The blood showed a greatly diminished number of platelets (22,000 per cmm.), and the coagulation time was not definitely retarded. A reduction in platelets does not occur in hemophilia. Owen observed a case of this type in a girl aged eleven, who had hemorrhages for twelve months, first from the bowels, then from the nostrils, and afterward from the left ear. There was no history of bleeders in her family, no arthritis, and no purpura.

[1] *Jour. Am. Med. Assn.*, 1906, xlvii, 1090.
[2] *Am. Jour. Med. Sci.*, 1895, cx, 631.

Diagnosis.—The Symptom.—Flea bites may closely simulate true petechiæ. Henoch says that in examining children on their admission to the hospital he has often been in doubt whether the hemorrhagic spots present were due to flea bites or to the hemorrhagic diathesis. Flea bites are quite small and usually show a central point the result of trauma.

Telangiectatic spots may be mistaken for purpura at the time of the first examination of a patient. Petechiæ quickly fade and disappear, while telangiectatic spots remain indefinitely. Furthermore, on palpation of the latter the color usually disappears momentarily or is replaced by a brownish stain. A case of generalized telangiectasis was admitted to the hospital with abdominal colic. He was tossing about the bed in agony, and it was impossible to obtain a satisfactory history owing to his condition. The telangiectatic spots were mistaken for petechiæ, and in view of the fact that he was passing bloody urine and suffering from colic, the disease was regarded as Henoch's purpura. Occasionally telangiectasis associated with recurrent hemorrhages from the mucous membranes is mistaken for chronic purpura.

Erythema exudativum multiforme is sometimes diagnosed as purpura. Physicians as well as students forget that if the color disappears on pressure the lesion is erythematous and not purpuric. It is well to use an ordinary glass microscopic slide for making this test.

The Disease.—There is danger of mistaking infectious diseases with hemorrhagic manifestations for idiopathic purpura. At the onset of a case of purpura with fever this possibility should be borne in mind. Without doubt many cases of acute lymphatic leukemia and aplastic anemia with symptomatic purpura have been mistaken for purpura hemorrhagica. The symptoms and clinical course of the rapidly fatal cases of leukemia, with little or no enlargement of the lymph nodes, may be indistinguishable from the morbus maculosus of Werlhof. *An examination of the blood should be made in every case of purpura.*

Scurvy and purpura have frequently been confounded. The chief diagnostic sign of scurvy is not bleeding from the gums, as is commonly taught but a brawny hemorrhagic infiltration of the thigh or lower leg—the so-called scorbutic scleroderma. Bleeding from the gums is not uncommon in purpura; in fact, it was noted in 23 of this series. Sponginess of the gums, on the other hand, is characteristic of scurvy and very rare in purpura. If the patient is well nourished and has had a varied diet, scurvy can be excluded. In some cases the diagnosis can only be made by observing the therapeutic effect of the addition of fruit and fresh vegetables to the diet. In scurvy there will be speedy and marked improvement.

Hemophilia is a hereditary and congenital disease limited to males as Bulloch and Fildes have shown. The family and past history are of diagnostic significance rather than the severity or the duration of the bleeding at the time of observation. As it is now known that there is a greater delay in the coagulation of the blood in hemophilia than in any other condition, it would seem that a definite diagnosis can be made in any suspected case. The blood platelets are not diminished, and the blood clot retracts normally.

Prognosis.—In purpura complete recovery is the rule, but the favorable course of mild cases is often interrupted by a relapse. When all the spots of hemorrhage have faded and all bleeding ceases and convalescence seems established then a new eruption may appear. In some cases relapse follows relapse. Every transition is seen from the light cases of purpura simplex in which the patient continues at his work and suffers no inconvenience to the fulminating cases which end fatally in 18 or 24 hours. In nephritis and cerebral hemorrhage, not in loss of blood, lies the chief danger of purpura. The prognosis in Henoch's purpura is better in children than in adults. Among 102 cases of Henoch's purpura (the present series combined with that of v. Dusch and Hoche, and cases collected by Macalister[1] from the records of Guy's Hospital), 8 resulted fatally. One of our series died of cerebral hemorrhage at the age of sixteen after repeated attacks during a period of seven years. Motor aphasia developed suddenly, and when brought to the hospital she could not speak and the right arm was weak; convulsions developed later. An exploratory operation was performed, and the brain and subpial space were of a uniform cherry color. Death occured four days later. In 4 of our 14 fatal cases death was due to cerebral hemorrhage. Osler has called attention to the seriousness of nephritis in the angioneurotic group of cases. Of the 7 deaths in a series he reported 5 were with uremia. The cases of nephritis can be divided into three groups: (1) Acute course with dropsy and death in uremia within three months. (2) Albumin disappears and recovery takes place. (3) The nephritis becomes chronic. Most of the cases belong in the second group. Recovery is the rule, even when the albuminuria exists for six months or longer. The development of chronic nephritis is rare. Osler[2] has recently reported three cases, and described the special features of this type of nephritis. A mild hematuria may persist long after the skin symptoms have disappeared. The albumin is usually abundant. Casts may be absent or scanty. There may be no œdema.

Treatment.—Rest in bed is of the utmost importance. Patients should not be allowed to sit up until some time after purpuric spots have ceased to appear. The sooner the patient leaves his bed the greater the liability to hemorrhage. In some cases extensive purpura disappears and hemorrhage from mucous membranes ceases quickly and completely after the patient is put to bed. That there may be little or no change in the general condition to account for the improvement has been shown by Duke who found that although all hemorrhages had ceased a prick of the ear would bleed for several hours. He found that ambulatory patients in whom the blood changes were slight had more bleeding into the skin and from the mucous membranes than the severer cases in the hospital wards.

The attendants should be impressed with the importance of handling the patient gently, as slight pressure on any part of the body is sometimes followed by bleeding into the skin.

The diet should be light and varied during the active state of the disease.

[1] *Guy's Hospital Gazette*, 1906, xx, 176.
[2] *British Medical Journal*, 1914, i, 517.

Fresh fruit and vegetables should be given. During convalescence foods rich in iron are indicated.

Many drugs have been employed but they are all of doubtful value. Sulphuric acid has been used since the time of Werlhof. Aromatic sulphuric acid is the preparation of choice; ℥xv to xxx (1 to 2 cc.) largely diluted, thrice daily. Osler advises oil of turpentine, 1 cc. (℥xv) three or four times a day. Ergot is still advocated in the treatment of purpura by some authors but there is no evidence that it does good and its employment on theoretical grounds is unjustifiable. It is asserted that calcium chloride and calcium lactate are often beneficial in purpura but this claim rests on no strong foundation. The coagulation time in purpura is rarely delayed, and Addis has shown that the coagulation time is unaffected by the administration of calcium salts by the mouth. In some of our severe cases calcium salts were given without effect. Calcium chloride has an unpleasant taste and hence the lactate is preferable. The dose is gr. xv (1 gm.) three or four times a day. Von Noorden recommends injections of calcium gelatin (5–7 cc. of a 5 per cent. calcium chloride gelatin) combined with the internal use of calcium lactate. The solution of gelatin is used in various strengths (4–20 per cent.). It must be thoroughly sterilized as tetanus has resulted from the use of gelatin. In purpura hemorrhagica attended with great loss of blood direct transfusion has apparently saved life (Duke). The use of serum and other measures for checking severe hemorrhage are described under hemophilia.

HEMOPHILIA.

Definition.—Hemophilia is an hereditary constitutional anomaly limited to the male but transmitted by the female, characterized by a tendency to bleed from trivial cuts and bruises, and by a marked delay in the coagulation in the blood.

Nasse, professor of medicine at Bonn, published in 1820 his investigations on hemophilia. He asserted that males alone are bleeders and the the disease is transmitted by normal females through their marriages with normal males. The limitations of the disease to males and the transmission through unaffected females is known as "Nasse's law."

The entire literature on the hereditary aspects of hemophilia has been subjected to a thorough critical analysis by Bulloch and Fildes.[1] In their monograph all the facts known concerning heredity in hemophilia have been collected and analyzed in a study remarkable for its thoroughness and its searching criticism.

Occurrence.—Hemophilia has been termed by Grandidier "the most hereditary of the hereditary diseases." It is rare in individuals who do not have a family history of bleeding, and a striking feature is the occurrence of a large number of cases in the same family.

In the remarkable Mampel family of Kirchheim, near Heidelberg, the disease has been carefully studied for nearly a century. The first report was published by Chelius in 1827, then by Mutzenbecher in 1841, by

[1] *Treasury of Human Inheritance*, London, 1911, xiv a, 169.

Lossen in 1876, and by Lossen again in 1905. Of the 111 male members of that family, 37 have been bleeders (33⅓ per cent.). Excluding those branches of the family that contain no bleeders, the number of affected male individuals rises to nearly one-half. In the first generation it was 50 per cent., in the second 68 per cent., in the third it fell to 41 per cent., and in the fourth to 32 per cent. In the little Alpine hamlet of Tenna the disease has existed through six or seven generations, and Vieli found 15 to 20 hemophiliacs living there at one time. Until the publication of the monograph of Bulloch and Fildes it was generally held that hemophilia affected

FIG. 55

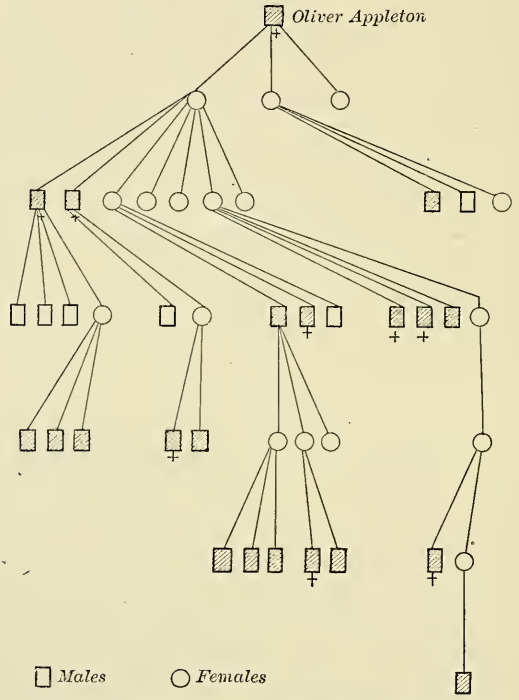


Chart of the Appleton-Swain family of bleeders, showing the transmission of the tendency to the seventh generation within two hundred years. The shaded figures represent bleeders and the cross a death from hemorrhage.

females as well as males. Grandidier's collection of cases contained 48 female bleeders, and Stempel found 42 cases of hemophilia in the female sex reported between 1890 and 1900, the ratio of males to females being 4 to 1. As Osler says, Karl Pearson's new "iatromathematical school of medicine" has taught the profession to be more careful about its facts as well as its figures. Bulloch and Fildes, in a study of 900 papers on hemophilia, found no case described in a female which bears more than superficial resemblance to the disease as seen in the male.

They found only 44 families reported with pedigrees in which the evidence seemed conclusive that hemophilia existed. Out of a total of 171

recorded instances of transmission 160 conform to the "law of Nasse;" the disease being transmitted by the unaffected female—the "conductor." Intermarriage has been common among hemophilic families so that a woman supposedly normal, but in reality a conductor, may marry a man in a bleeder family and transmit the disease to his sons. This is the explanation Bulloch and Fildes offer for the 11 cases in which it has been claimed that the disease was propagated through the male.

The remarkable fertility of the women in bleeder families was first noted by Wachsmuth. In the series of genuine cases analyzed by Bulloch the average number of children was six. Of the 125 mothers who had sons, 37 did not transmit the disease and 39 had no normal sons. If the published statistics are correct the proportion of males in hemophilic families is much higher than normal. The marriage rate of the males who are bleeders is low compared with similar rates in the females.

The form of *heredity* seen in hemophilia is not peculiar to this disease. In color blindness and also in night blindness transmission is likewise through the females, while the male alone exhibit the abnormality. Gee has observed a similar mode of transmission in diabetes insipidus, and it is said to occur in ichthyosis and in pseudohypertrophic muscular paralysis. The disease is much more common in northern countries than in southern. About twice as many cases have been observed in Germany as in any other country. Comby, an authority on the disease, comments on the rarity of its occurrence in France.

The Delayed Coagulation of the Blood.—As was shown by Wright in 1894 and confirmed by subsequent investigators, the coagulation of the blood in hemophilia is greatly prolonged. All are agreed that the defect in coagulation is the only constant pathological sign of the disease. Addis shows that there is a direct relation between the severity of the symptoms and the degree of retardation of the coagulation. In order to understand recent studies of the blood in hemophilia, it is necessary to present briefly the current theories of coagulation of the blood. All investigators are agreed on a few points. The coagulation of the blood consists in the formation of an insoluble substance, called fibrin, from an albuminous body, the fibrinogen, which is dissolved in the plasma. A substance called prothrombin or thrombogen is also present in plasma. The presence of calcium is necessary for clotting of the blood to take place. There is no thrombin, the so-called fibrin ferment, in the circulating blood. This is formed when blood comes in contact with foreign bodies. In serum any thrombin that may be present is slowly neutralized by a body called antithrombin.

Morawitz's theory is the one most generally accepted. Thrombogen or prothrombin is converted by a body called thrombokinase in the presence of calcium into thrombin, which, by its action on fibrinogen forms fibrin. Thrombogen is derived from blood platelets; thrombokinase from all cellular elements.

Howell's theory. Prothrombin is activated to thrombin by calcium alone. Antithrombin is present in the circulating blood and binds the prothrombin. When blood is shed thromboplastin is formed from injured cells of the tissues or from platelets, and combines with antithrombin.

Thereby prothrombin is freed and coagulation begins. Howell denies the existence of thrombokinase. He holds that the substance in the tissue that accelerates clotting acts not on prothrombin in the manner of a kinase but by neutralizing the antithrombin.

Nolf's theory. Coagulation is a physico-chemical change due to the interaction of three colloids—fibrinogen, thrombozyme, and thrombogen. These unite to form fibrin and thrombin. According to Nolf, thrombin is not the cause but only a product of coagulation, being a part of the fibrin which remains in solution. Thrombozyme is a body derived from the endothelium, leukocytes, and platelets. It is similar to Morawitz's thrombokinase. The fibrinogen and thrombogen are formed in the liver and are free in the circulating blood.

Cause of the Delay in Coagulation.—This is not due to a deficiency in fibrinogen, for the clot when it forms is of normal firmness. Furthermore, Sahli has weighed the fibrin produced in hemophilic blood and found it normal, and Addis has shown that hemophilic fibrinogen coagulates as readily as normal fibrinogen. The fault lies in some disturbance in the formation of the so-called fibrin ferment, thrombin. According to Morawitz's theory three bodies combine to form thrombin. These are thrombogen, calcium salts, and thrombokinase. Sahli and Morawitz think the first two are present in sufficient amount, but that thrombokinase is not given up by the cellular elements in a normal manner. Thrombokinase, according to Morawitz, is a general product of protoplasm and is formed by the endothelium of the bloodvessels as well as by other tissues, when cut or otherwise injured.

Sahli believes that in hemophilia there is fermentative defect of the whole protoplasm of the body. This would make hemophilia a diathesis in the strictest sense of the word. According to this view, hemophilia is due to an inherited defect in the formation and utilization of the thrombokinase. Sahli holds that the long continued bleeding results from the failure of the cut vessels to yield the normal quantity of thrombokinase. Gressot found that extracts of the organs of a hemophilic, with the exception of the skin, accelerated markedly the coagulation of the blood. This would seem to disprove Sahli's contention that the organs contained a deficiency of thrombokinase. Addis concludes that the thrombokinase in hemophilia is as abundant and active as in health. He believes that the defect in hemophilic blood is in the prothrombin, which although present in normal amount, is changed in character so that a longer time is required for the formation of thrombin; hence the delay in the coagulation of hemophilic blood.

Nolf and Herry maintain that hemophilia is due to a qualitative defect in a substance essential to coagulation that is formed in the leukocytes, platelets, and vascular endothelium. This body, which they call thrombozyme, is similar to the thrombokinase of Morawitz. Weil attributed the delay in coagulation to an excess of antithrombin, while Wright held that it is due to lack of calcium. Later investigators have found the antithrombin and calcium present in normal amounts.

Howell's experimental studies convinced him that the delayed coagulation of the blood in hemophilia was due to the prothrombin, which was

either altered in character or deficient in quantity. He prepared prothrombin from hemophilic blood and found that there was no delay in its conversion into thrombin. As this finding overthrew the idea that prothrombin had altered properties, Howell concluded that the delay in coagulation of hemophilic blood is due to a diminution in the amount of prothrombin.

The Coagulation Time.—The blood should be obtained directly from a vein by means of a needle as the capillary blood from a skin puncture with its admixture of tissue juice may fail to show the characteristic delay in coagulation.

In one of Howell's cases the coagulation time of 2 cc. of blood with which, owing to defective technique, some tissue juice was mixed, was 10 minutes. The same amount of blood obtained at the same time directly from a vein had a coagulation time between 4 and 5 hours. In another of Howell's cases the coagulation time of the capillary blood had been recorded as only 6 to 12 minutes, while 2 or 4 cc. of venous blood began to clot in 3 to 4 hours and 4 to 5 hours were required for complete clotting. The negative results of earlier investigators were probably due to the fact that they made their tests with blood from a bleeding wound or skin puncture. The studies of Addis would seem to show that with proper technique trustworthy results can be obtained with blood from skin punctures. The method chiefly used by him was a modification of that described by McGowan and the tests made at a temperature of 20° C. Under these circumstances normal blood coagulates in ten minutes. There was a delay in the coagulation of hemophilic blood far exceeding any retardation of coagulation observed in other diseases. He compared McGowan's method with that of Morawitz and Bierich and the results agreed very well. The coagulation time of blood from skin wounds in the twelve cases studied by Addis ranged from 15 to 85 minutes. In nine of the twelve the shortest coagulation time was 54 minutes. His patients descended from six hemophilic stocks in Scotland, England, and Germany.

In the case studied by Morawitz and Lossen the coagulation of 2 cc. of blood began in 76 minutes, but the time for complete coagulation was 110 minutes. In a case of hemophilia studied by Vogel in which the disease was not hereditary the coagulation time of the venous blood was 88 minutes.

Methods of Determining the Coagulation Time.—*Venous Blood.*—1. Morawitz and Bierich. The blood is obtained by puncturing a vein and 2 or 5 cc. are placed in a carefully cleaned and dried watch glass. This is placed in a moist chamber provided with a thermometer. The moment when on tipping the watch glass, the surface of the blood no longer moves is taken as the end of the coagulation. Normally the time ranges from 15 to 20 minutes at a temperature of 20° to 22° C. 2. Howell places 2 to 4 cc. of blood in wide tubes 21 mm. in diameter. The moment when the clot is firm enough to permit inversion of the tube is selected as the end point. Normal blood tested by this method clots usually in from 20 to 40 minutes at room temperature.

Capillary Blood.—1. Duke's modification of Milian's method. A microscopic slide on which are mounted two glass discs 5 mm. in diameter

is the only apparatus required. Drops of blood large enough to cover each disc are taken and the slide inverted over a glass of warm water (38° C.) After coagulation has proceeded to a certain degree the contour of the drop does not change when the slide is held in a vertical position. The coagulation time of normal blood varies from 6 to 9 minutes.

2. Rudolph's modification of McGowans's method. Thin glass tubes 1.5 cm. in inside diameter and about 18 cm. long are used. A pint thermos bottle is provided with a rubber stopper in which three holes are made. In two of these rest brass tubes just large enough to hold the glass tubes. A thermometer is inserted in the third perforation. The bottle is filled with water at 20° C. and rests on its side. Two glass tubes are partially filled from a drop of blood obtained by a prick of the finger. Each tube is at once placed in one of the brass tubes of the thermostat and the protruding ends sealed with an alcohol lamp. In about five minutes the first tube is withdrawn and broken near the open end of the tube. If the blood is still fluid the tube is replaced in the thermostat. When a thread of fibrin is seen on slowly separating the broken pieces of the tube the end point has been reached. At 20° C. the average coagulation time is about eight and one-half minutes.

Howell's Method of Examination for Prothrombin.—This procedure according to Howell gives a convenient and trustworthy method of diagnosing hemophilia. Blood is withdrawn from a vein by means of a Luer syringe. Four cc. are emptied into a centrifugal tube containing 0.5 cc. of 1 per cent. solution of sodium oxalate (made up in a 0.9 per cent. solution of sodium chloride). After mixing by inverting the tube, centrifugalize at high speed until a clear plasma is obtained. Five drops of oxalated plasma are placed in each of four tubes and to these are added in series, 2, 3, 4, and 5 drops of a 0.5 per cent. solution of calcium chloride, with the object of obtaining in one of the tubes the optimum concentration of calcium. Tested by this method, the clotting of normal blood plasma is remarkably uniform, varying between 9 and 12 minutes. The clotting time for hemophilia was greatly delayed. In Howell's cases it was never less than 90 minutes.

Symptoms.—The essential characteristic of hemophilia is the occurrence of severe hemorrhages following such slight injuries that in a normal person little or no bleeding would result. There is no tendency for the hemorrhage to stop in the usual manner. Epistaxis is common in bleeders but it is so frequently seen in other conditions that its occurrence alone, even when repeated and the bleeding severe, does not justify the diagnosis of hemophilia. The umbilicus at birth is seldom the site of bleeding in hemophilia (Bulloch and Fildes.) Tooth extraction has been responsible occasionally for death from hemorrhage but it is unjustifiable to assume from this that hemophilia existed.

Spontaneous hemorrhages probably do not occur. Although there may be no evidence of trauma the so-called spontaneous hemorrhages are usually in a position exposed to slight blows or pressure. Sometimes the most trivial injury, such as pressure of the hand on the skin or the rubbing of clothes on the body, has been followed by hemorrhage. The skin lesions vary from a bruise to a hematoma. Ecchymoses and sugillations

are uncommon; they are sometimes incorrectly described as purpuric spots.

The tendency to hemorrhage is always chronic and is noticed in early childhood. If adult life is reached the bleedings may decrease in frequency and severity. Variations in the liability to hemorrhage may occur from week to week. At one time pressure of the finger will produce a black and blue spot, later the same amount of pressure may not produce a bruise and a cut may not bleed unduly.

The cases of hemophilia are divided by Addis into three groups. In the first the patients are scarcely ever free from hemorrhage into the skin or elsewhere, even in the absence of any trauma greater than that inseparable from ordinary life. In the second group trivial accidents do not lead to hemorrhage. In the third group bleeding persists for a longer time than in a normal person, but the excessive bleeding only results when the injury is sufficient to produce an appreciable amount of hemorrhage in a healthy individual. The retardation of the coagulation varies with the severity of the case. Nine of the twelve cases investigated by Addis belonged in the group with severe symptoms.

The real distinction between a hemophilic and a normal person is not the occurrence but the amount of the bleeding. When the tissues of a normal individual are slightly injured by a blow a few capillaries are ruptured but these are quickly sealed and there is no apparent hemorrhage. A similar blow applied to a hemophilic will not cause any greater bleeding at the moment, but the hemorrhage continues for some time and considerable blood enters the tissues giving rise to a bruise or a hematoma.

The subcutaneous hematomas are sometimes painless, but may give rise to much suffering and be accompanied by fever and gastro-intestinal disturbances. Sometimes they reach a very large size, and may weaken the patient from loss of blood. In fact, death has occurred from hemorrhage into the tissues unassociated with external bleeding. Hamilton[1] observed a large hematoma of the head which did not disappear for over four months. A subcutaneous hemorrhage was seen by Fussell[2] in a child which reached from the axilla to the lower costal margin and from the mammillary to the scapular line. It is characteristic of hematomas in this disease, as Stempel has pointed out, that they tend to spread far from their point of origin. In Ross'[3] case the hemorrhage began at the elbow and gradually extended until it involved the entire upper arm. Pressure of the extravasated blood on the nerves may give rise to severe pain or paralysis. The pulse may be obliterated in consequence of arterial compression. Linser[4] reported a case in which paralysis of the hand followed the disappearance of a hematoma from its dorsal surface. Subfascial and intermuscular hemorrhages are rare, and even more unusual are hemorrhages into large serous sacs. Psoas-hematomas have been studied by Moses, but are of very rare occurrence. Sometimes in subcutaneous or intramuscular hemorrhage resorption does not occur and a cyst may form, as in a case reported by Virchow.

[1] *New York Med. Rec.*, November 20, 1891.
[2] *Brit. Med. Jour.*, 1897, ii, 1230.
[3] *Ibid.*, April 2, 1898.
[4] *Beit. z. klin. Chir.*, 1896, xvii, 105.

Hematomas in bleeders have frequently been mistaken for phlegmons. Sometimes the differential diagnosis is impossible. Gayet[1] reported a case in a twelve-year-old bleeder in which pain and swelling of the left arm suddenly developed. The swelling rapidly increased, the overlying skin was glossy, tense, and extremely tender. The temperature rose to 102° and the diagnosis of an acute phlegmon was made. Later a second swelling appeared which gave a distinct sensation of fluctuation. An incision was made, but instead of pus only sanguinolent fluid and blood clots were found.

A trivial wound or a mere scratch may be followed by a more serious hemorrhage than a clean cut. This has been noted by many observers. Fordyce claims that he checked a hemorrhage by enlarging the wound with a knife, but this procedure cannot be recommended in dealing with lacerations which bleed seriously, for the reason that fatal hemorrhage has repeatedly occurred during surgical operations on bleeders. The attempt to amputate the bleeding part or to tie an artery in cases of uncontrollable hemorrhage has been followed by death. The blood drips from a wound as it would from a blood-soaked sponge. This type of hemorrhage is often described as parenchymatous, and spurting arteries are never seen. It was noted among the Appleton-Swain family that if several cuts had been inflicted at the same time severe hemorrhage occurred from only one.

The hemorrhage usually lasts for hours, and it may continue for days or even weeks. Litten mentions the case of a bleeder who, within eleven days, lost twenty-four pounds of blood. Bleeders have been repeatedly observed who recover from almost lethal hemorrhages with extraordinary rapidity. After severe, long-continued hemorrhage the blood may be almost colorless. One observer states that it would scarcely stain linen. Wounds in bleeders often heal very slowly, and the resorption of blood in interstitial hemorrhages may be long delayed. In fractures of bone union may take place in the usual time (Monsarratt).[2]

Joint Affections.—They occur with such great frequency that some authors, in their definition of the disease, have mentioned the association of joint swelling with the hereditary tendency to uncontrollable hemorrhage. Linser is probably right in his statement that those bleeders who have not had joint complications are the exception. It can be asserted with a good deal of confidence that all the different joint affections from the slightest arthralgia to the severest hemarthrosis are due to hemorrhage from the synovial membrane into the joint cavity (Stempel).

König's[3] classification of the hemophilic joints into three stages is generally followed: first hemarthrosis, the stage of hemorrhage; second, the inflammatory stage which resembles closely hydrops tuberculosus fibrinosus; third, contraction, scar formation, and ankylosis. Hemorrhage into the joint may take place rapidly, and sometimes within five or ten minutes it becomes greatly swollen. The position of slight flexion or extension may be assumed, but if the blood is absorbed rapidly the affection will not pass into the second stage and the function of the joint may

[1] *Gaz. hebd. de méd. et de Chir.*, 1895, vol. xxxii, 258.
[2] *Brit. Jour. of Child. Dis.*, 1904, vol. i, 494.
[3] *Volkmann's Sammlung klin. Vorträge*, 1892, Neue Folge, Nr. 36.

not be disturbed. There may be repeated hemorrhages and all be promptly resorbed. Gocht[1] reported a case in which the patient had more than forty-five severe hemorrhages into the right knee-joint. The blood in each instance had been quickly absorbed and the usefulness of the joint had been but slightly impaired. The left knee-joint, which was contracted, had been the site of about forty hemorrhges, the first thirty-nine being well borne, but the last gave rise to the deformity.

Probably none of the joint hemorrhages is really spontaneous in origin, although some have occurred while the patients were at rest in bed. The thin-walled vessels of the hyperplastic synovial fringes might readily be ruptured by a simple movement of the bone, as has been pointed out by Linser and Litten. Small as well as large joints may be affected, and hemorrhges have occurred into the small joints of the fingers and toes. The large joints, especially the knee and elbow, are most frequently involved. Among 32 cases collected by Piollet[2] the knee was involved in every instance, the elbow 6 times, and the ankle 12 times. Pain in the joint bears no direct relation to the degree of swelling. The pain may be severe, but in some cases even with marked swelling it has been absent. Fever frequently accompanies the joint attacks. A maximum temperature of 101° or 102° is not uncommon. Sometimes the pain disappears before there is any reduction in the swelling. A few cases have been reported in which the blood disappeared with extraordianary rapidity. In one described by Klemperer the swelling which occurred in the morning disappeared in the evening of the same day. Usually the effusion persists for days or weeks. Spontaneous dislocation of the joint may occur, but there is rarely a high degree of crippling. Linser's case exhibited greater deformity than any other reported; both knees were ankylosed in a position of acute flexion, so that the patient was unable to walk.

Neuralgia and *neuritis* are common in hemophilic patients. These symptoms may be explained in part by the pressure of the effused blood on the nerves. Occasionally long-continued fever has been observed which could not be explained by any local finding.

Diagnosis.—Many conditions are mistaken for hemophilia, but a genuine case of this disease is rarely confused with anything else. It should always be borne in mind that hemophilia is a hereditary disease and one that manifests itself in early childhood. No single hemorrhage, no matter how severe, will warrant the diagnosis of hemophilia. The examination of the blood is of great importance as it has been clearly shown that the coagulation time is markedly delayed in hemophilia. In any suggested case the coagulation time of the blood should be determined by an approved method. More trustworthy results are obtained with venous than with capillary blood. The blood should be drawn from a vein of the arm through a hollow needle. Experience has shown that there is no danger of excessive hemorrhage from this procedure.

Chronic purpura hemorrhagica has frequently been confused with hemophilia. In the former the platelets are reduced in number and the coagulation time normal, while in hemophilia the coagulation is greatly delayed

[1] *Verhandl. d. deut. Gesellsch. f. Chir.*, 8 Kongress, 1899, 359.
[2] *Gaz. d. hôp.*, 1902, No. 39, 385.

and the platelets are normal. In purpura hemorrhagica the blood clot loses its power of retraction and there is no transudation of serum, while in hemophilia the retraction of the clot and the transudation of serum take place in normal manner (Hayem).

The writer saw two cases of chronic purpura with J. W. Coe in New York which, without the aid of the blood examination, might easily have been mistaken for hemophilia. The first patient was a youth aged seventeen years. The family history was entirely negative. Since the age of five years he had had frequent profuse attacks of epistaxis recurring at irregular intervals, sometimes lasting for hours and causing him to faint. The gums and mucuous membrane of the mouth at times oozed blood. The severe attacks had usually been accompanied by numerous purpuric spots over the face and extremities. He had frequent attacks of rheumatoid pains in the knees, usually accompanied by fever, and an outbreak of petechiæ on the legs. The slightest bruise was invariably followed by an ecchymosis. After having a tooth pulled he bled profusely for three hours. The second was a man aged thirty-two years in whom there was no family history of hemophilia. When six years old he bled profusely for hours after having a tooth pulled, and two years later began to suffer from frequent attacks of epistaxis, which continued until he came under observation. Any slight bruise was always followed by a subcutaneous hemorrhage.[1] The coagulation time in these patients was normal. The number of blood platelets was found to be greatly reduced, even at a time when the patients were free from hemorrhage (one 29,000 per cmm. and the other 22,000 per cmm.; the normal being about 450,000).

The so-called purpura rheumatica is sometimes confused with hemophilia, but the joint affections of the two are entirely different. There is not a single case on record in which the joint affection in hemophilia has been demonstrated to be other than hemarthrosis, while there is not a single case of undoubted purpura rheumatica in which hemorrhage into the joint has been proved. The joint swelling of hemophilia may simulate tuberculosis very closely. The value of tuberculin in such cases was well shown by König[2] in a patient who, in addition to the joint affection, suffered from lupus and tuberculous epididymitis. The lupus and the epididymitis reacted markedly to tuberculin, while the affected joint did not show the slightest reaction. The diagnosis of a hemophilic joint is confirmed by the appearance of ecchymoses beneath the skin subsequent to the swelling.

Prognosis.—Every hemorrhage in an individual in whom the hemophilic tendency is pronounced endangers life, but bleeders rarely die from their first hemorrhage (Osler). Childhood is the most dangerous period, and the old view that children rarely died during the first year cannot be held any longer, as in the collection of cases by v. Etlinger[3] more deaths occurred during the first year than at any other time. According to Grandidier, among 152 hemophilic boys, 81 died before the end of the seventh year. With sufficient care middle life would seem to be within

[1] *Jour. Am. Med. Assn.*, October 6, 1906.
[2] *Volkmann's Sammlung klin. Vorträge*, 1892, Neue Folge, Nr. 36.
[3] *Jahrb. f. Kinderheilkunde*, 1901, liv, 24.

the reach of many bleeders (Legg), and the longer one survives the greater the chance of outliving the tendency. This favorable termination is unfortunately rare, and Legg was able to collect only 9 cases, although there are instances in which bleeders have lived to old age. As the disease presents itself in manifold types varying from the mild to the severe, the prognosis in each individual case is to be based solely on the patient's past experience and that of his family.

Treatment.—No surgeon should begin an operation and no dentist should pull a tooth until it has been ascertained that the patient is not a bleeder. In hemophilic families the children from birth should be protected from every injury, and no surgical operation should be allowed. Running, jumping, and active games should be forbidden. The teeth should receive most careful attention, but no tooth should be pulled. Bleeders should always live the simple life, and aim by ordinary hygienic measures to increase their strength and vitality. The disease is extremely rare in warm climates, and residence in the South during the winter should be advised. Comby states the case of a patient who bled profusely in Paris, but when taken to Nice the hemorrhages stopped only to recur again upon returning to Paris.

Remarkably good results were claimed by Wright with calcium chloride and calcium lactate, but in the experience of recent writers the calcium salts did not definitely lessen the hemorrhagic tendency.

Upon the onset of hemorrhage compression is naturally the first thing to try if the site of bleeding is accessible. Plugging the nostrils or packing the uterus with tampons is frequently necessary. Many writers advocate the application of ferric chloride to the bleeding surfaces, but it is usually ineffectual. Hemorrhages have been repeatedly checked by the application of gauze compresses soaked with a sterile solution of gelatin. Sahli employed a 2 per cent. gelatin solution, but a 5 per cent. solution is recommended by other writers. Gelatin given by the mouth is of questionable value; it has been given frequently with fruit juices. This method of administering gelatin is harmless, but the same cannot be said of the subcutaneous injection. Not only is this procedure painful, but gelatin may contain tetanus spores which are not destroyed except at a very high temperature. Furthermore, severe hemorrhage may be produced in hemophilia from the puncture wound made in injecting the gelatin. If gelatin is employed subcutaneously or applied locally to the wound, great care should be taken to sterilize it thoroughly. The experiments of Boggs failed to show that gelatin reduced the coagulation time of the blood. It is quite possible, as Sahli suggested, that the gelatin solution applied to the bleeding surface under pressure, such as is exerted by the bandage, enters the mouths of the open vessels and there favors the union of thrombogen and thrombokinase.

Schäfer has recommended the addition of calcium chloride and adrenalin to styptic lotions. Among other measures that may be resorted to for checking the hemorrhage are the actual cautery, and 1 to 10 per cent. solutions of cocaine and 1 to 1000 adrenalin.

Perthes checked severe hemorrhage from the gums which had lasted three weeks, by the injection of defibrinated blood of a rabbit into the

tissues about the bleeding point. Bleeding recurred, but was controlled by the application of gauze soaked in defibrinated rabbit's blood. Bienwald withdrew some blood from the median vein of a healthy person and injected it quickly into the bleeding wound of a hemophilic patient. The foreign blood coagulated and prevented further hemorrhage. He believes that hemorrhage might be stopped by the injection of healthy blood into the tissues about the wound.

The injection of normal serum in hemophilia was first employed by Weil. He obtained remarkably good results, and within a short time this method came into general use. The injections have been given subcutaneously, intramuscularly, and intravenously. The usual dose is 10 to 20 cc. of fresh serum, intravenously or 20 to 30 cc. into the tissues. As fresh serum accelerates clotting *in vitro* much more than older serum, it is advisable to employ serum as fresh as possible. Human serum is preferable, but horse serum and rabbit serum have been frequently used. Serum not hemolytic to the hemophilic blood should be obtained. Antidiphtheritic serum has been employed as a substitute for fresh serum because it is so readily obtaiend, but as experiments on hemophilic blood outside of the body show that such old serum retards the coagulation time its use cannot be recommended. Some writers have advocated defibrinated blood. Gressot, Schloessmann and other writers state that they have had no success with serum. One of Schloessmann's patients had serum disease after the third injection of rabbit serum and defibrinated blood.

The use of Witte's peptone was introduced by Nolf and Herry into the therapy of hemophilia. They regard it as more efficient than serum. Although peptone when introduced into the circulation in large amount renders the blood non-coagulable, in small amount it is held by Nolf and Herry to act as an antigen, and by its action the vascular endothelium and the leukocytes produce more thrombozyme and thromboplastic substance. In one case of hemophilia they obtained by the method marked acceleration in the coagulation of capillary blood without notable change in the clotting of the blood from a vein. Tixier and Nobecourt report good results from its use. The solution was prepared as follows: Witte's peptone, 5 gm.; sodium chloride, 0.5 gm.; distilled water, 100 cc. This is sterilized and 10 to 20 cc. are injected subcutaneously. It may give rise to considerable pain at the site of injection and slight elevation of temperature. The injections may be repeated every two or three days if necessary. Fatal hemorrhages have been attributed, in one case recently reported, to an intolerance toward peptone that manifested itself after the twelfth injection (Lereboullet and Vaucher[1]). In the treatment of hemophilia Nobècourt and Tixier, whose experience has been relatively large, have never observed any serious complications from the use of peptone when the following technique was used. A series of four to six subcutaneous injections of 3 to 5 cc. of peptone solution is given. Before beginning another series an interval of three to six weeks should elapse.

[1] *Bull. Soc. de pédiat. de Paris*, 1914, No. 3, 132.

PART III.

DISEASES OF THE LYMPHATIC SYSTEM.

CHAPTER XVIII.

DISEASES OF THE LYMPHATIC GLANDS.

By ALDRED SCOTT WARTHIN, Ph.D., M.D.

General Considerations.—The great majority of the diseased conditions of the lymphatic glands are *secondary* in nature, and are the direct result of the part played by the lymphoid structures in the protection of the body. In the exercise of their function as *filters* of the lymph stream, whereby they remove from the latter substances gaining entrance into the lymphatic vessels, their own integrity is often sacrificed to the welfare of the organism as a whole. Into the lymph stream of any region of the body a great variety of formed elements may pass, such as dust, carbon, bacteria, disintegrating blood cells, blood pigment, dead tissue cells, inflammatory exudates, tumor cells, toxic substances, etc. Usually the regional lymph nodes filter out such foreign substances and retain them either permanently or temporarily, in some cases rendering them harmless or destroying them, while in other cases the injurious agent is able to cause degeneration or necrosis and inflammation within the lymphoid tissue itself. In this conflict, particularly when pathogenic bacteria are concerned, the lymphatic glands may suffer severe inflammatory processes, even to the extent of total destruction by suppuration; but in the great majority of cases the infective agent is disposed of by the gland after a more or less marked local inflammatory reaction. *Lymphogenous lymphadenitis* due to local primary infections, becomes, therefore, the most important and common affection of the lymphatic glands.

Since the involvement of the regional lymph glands is usually secondary to some primary infection within the region tributary to them, we find, for example, involvement of the axillary and cubital glands in the case of infections of the hand, arm, or mammary gland, involvement of the cervical glands in infections of the mouth cavity and pharynx, of the bronchial glands in pulmonary infections, etc. Such an involvement of the regional lymph glands occurs also in chronic inflammations of the corresponding regions and in the case of malignant tumors occurring therein, particularly carcinoma.

Hematogenous secondary affections of the lymphatic glands also occur, but are relatively much less frequent than the *lymphogenous* conditions. Multiple or universal involvement of the lymph glands characterizes the hematogenous affections, whereas in the lymphogenous conditions one set of regional lymph glands is usually alone involved. The infective agent reaches the glands through the arteries, and the localization in the lymphatic glands is but an expression of a generalized process. Such hematogenous affections of the lymphatic glands are seen in syphilis, anthrax, diphtheria, and a number of other infectious diseases; indeed, hematogenous lymphatic involvement may occur in practically every one of the infectious diseases.

The *primary* diseases of the lymph glands are relatively rare compared to the secondary ones. With the exception of cryptogenic primary infections, they consist almost wholly of *hyperplastic* and *tumor-like* conditions showing a more or less malignant and progressive course. They may involve all the lymph glands of the body, or only regional groups. Their clinical classification is confused, their etiology unknown, and different authorities are not agreed as to their pathological nature. To this class of primary lymphatic affections belong the various conditions of the lymph glands known as Hodgkin's disease, adenia, lymphadenia, lymphogenic diathesis, lymphadenosis, lymphoma, lymphocytoma, lymphomatosis, pseudoleukemia, leukemic and aleukemic lymphoma, lymphosarcoma, etc. Primary tumors of the lymph glands of a type other than that of the lymphoma or lymphosarcoma are very rare.

INFLAMMATION OF THE LYMPH GLANDS. LYMPHADENITIS.

Lymphadenitis Simplex.—In the majority of cases inflammation of the lymph nodes is the result of the entrance of bacteria or of poisonous substances into the afferent lymphatics. There is usually an associated lymphangitis, but it may be of so slight a degree as to pass unnoticed. While the condition of lymphogenous lymphadenitis is more often localized in a regional group of glands, the entire lymphatic system may be affected in cases of generalized infection or intoxication, and in such cases the inflammation is usually hematogenous in origin. Trauma alone has been thought to be sufficient to cause inflammation of the regional glands of the part or extremity involved, but in such cases infected scratches or cuts are usually present, or cryptogenic infection has occurred. Direct injury of the nodes is a relatively rare cause of lymphadenitis. On the other hand, no evidences of lymphadenitis may be found in the regional glands of an extremity showing ascending gangrene or marked cellulitis, because of the fact that the afferent lymphatics have become blocked with lymph thrombi that prevent access to the glands of either bacteria or their products.

The *inflamed* lymph gland is enlarged, swollen, its capsule stretched, and its bloodvessels hyperemic. Its consistency is at first soft, later more firm, unless suppuration occurs, when it may undergo a partial or complete liquefaction. On section the cut surface is moist, medullary

in character, homogenous, dark red or grayish with red mottlings or streaks corresponding to the injected bloodvessels, and from the cut surface an abundant grayish-red or bluish-red tissue juice can be scraped. In severe cases, particularly in the later stages, yellowish or grayish, opaque *focal necroses* may be seen throughout the gland substance. As the process becomes older the general color of the affected gland becomes paler, the surface less moist and the consistence firmer, owing to the new formation of lymphocytes and the increase of polymorphonuclear cells, whereby the lymph sinuses become blocked up. The periglandular tissue is also œdematous, hyperemic, and infiltrated.

On microscopic examination there is seen a lymphoid hyperplasia of the gland, enlargement of the germ centres with numerous mitoses, infiltration of the lymphoid tissue with polymorphonuclear cells, and dilatation of the lymph sinuses with a marked desquamation and swelling of the endothelial cells lining the sinus (*sinus catarrh*). Great numbers of lymphocytes and polymorphonuclear cells are found also in the meshes of the reticulum of the sinuses. The efferent lymphatics contain a great excess of cellular elements. In some cases the lymph sinuses may be distended with a fluid exudate poor in cells. Resolution of the inflammatory process may take place at this stage, the cellular exudate may undergo fatty degeneration, the remains of dead cells, blood pigment, etc., may be carried away or digested, and a complete restitution to the normal may occur. In this process the large endothelial cells of the sinuses play a very important part by their phagocytic action.

In severe inflammations small areas of degenerating or necrotic cells may occur throughout the affected gland. The nuclei of the cells in these areas may disappear, while the cells themselves become converted into hyaline or granular masses. The exudate in the lymph sinuses may exhibit a *croupous, croupous hemorrhagic*, or pure *hemorrhagic* character. The sinuses may become filled with a dense fibrin network, in the meshes of which lie swollen and desquamated endothelial cells, leukocytes, and red blood cells. Active phagocytosis on the part of the desquamated endothelium is usually evident. In other severe forms of lymphadenitis (typhoid fever) the degeneration or the necrosis often becomes very marked, so that a confluence of the focal necroses occurs, and the resulting dead area may take on the appearance of a caseation necrosis. The hemorrhagic and croupous forms occur especially in anthrax, diphtheria, typhoid fever, and bubonic plague. The necrotic form is very common in the mesenteric nodes in typhoid fever.

Lymphadenitis Purulenta.—In certain forms of lymphadenitis, particularly that due to pyogenic infection or to soft chancre, the affected lymph node becomes infiltrated with polynuclear leukocytes, which collect in the areas in which there is a primary degeneration or necrosis of the lymphoid cells caused by the infective agent. Liquefaction of these areas then follows, and abscesses are formed that not infrequently destroy the entire lymph gland and extend into the neighboring tissues (*purulent peri-adenitis*). Suppuration is often long delayed. Fluctuation is usually not obtained until the capsule of the gland has been broken through and the neighboring tissue involved in the suppurative process.

Staphylococci, Ducrey's bacillus and the gonococcus are the organisms most frequently concerned in the causation of purulent lymphadenitis.

Chronic Lymphadenitis.—Chronic inflammations of the lymph node not caused by any of the specific infections, may be due to the presence within the glands of healing abscesses or organizing necrotic foci, to excessive deposits of pigment, dust, etc., in the glands, chronic infections with bacteria of low virulence, absorption of poisons from areas of chronic inflammation in the region tributary to the glands, or from ulcerating or necrotic neoplasms, etc. Even when the neoplasm shows no secondary changes of this kind, the regional lymph glands are practically always in a state of chronic lymphadenitis, due possibly to the absorption of products of tumor metabolism. Chronic irritation of any kind in any given region causes chronic inflammatory changes in the corresponding lymph nodes. As examples, may be mentioned the chronic lymphadenitis due to carious teeth, adenoids, pharyngeal catarrh, eczema, etc.

Large abscesses or necrotic foci within lymph nodes are gradually replaced by connective tissue as the result of the chronic proliferative inflammation set up about them. The dead tissue is absorbed, granulation tissue takes its place, and with the change of the latter into scar tissue the affected node becomes hard and indurated (*lymphadenitis indurativa* or *proliferans*). The capsule is thickened, the sinuses more or less obliterated, and the lymphoid tissue replaced by fibrous connective tissue. Hyaline degeneration of the latter is very common. In case the dead tissue cannot be absorbed, it is encapsulated by connective tissue, and becomes inspissated or calcified. In the simple forms of chronic lymphadenitis the capsule and stroma are also usually thickened; but there may be a well-marked hyperplasia of the lymphoid tissue, the nodes being very rich in cells without otherwise suffering much structural change. Sooner or later the stroma increases at the expense of the lymphoid tissue, and the gland becomes smaller and indurated. The sinuses may be blocked by proliferating endothelium. The glands may become completely fibroid, or may suffer a fatty metaplasia.

Symptoms.—These in general or localized lymphadenitis are fever and malaise associated with painful swellings of the lymph nodes. In the purulent form the skin over the enlarged glands becomes red, circumscribed fluctuation may be recognized, and perforation may finally take place. High fever usually accompanies this form, but in some cases the general symptoms are mild, even when large abscesses are formed. The involvement of deep-lying nodes, between the fascia or muscles, is especially painful. In the general enlargement of the lymph nodes seen in many of the acute infections, all of the lymph glands may be enlarged, hard and shotty, and tender on pressure. In chronic lymphadenitis the only symptoms may be the gradual enlargement of the lymph nodes, usually without pain, although tenderness is often elicited by pressure, and finally the induration. As a result of a chronic perilymphadenitis the lymph nodes may become attached to the skin or surrounding structures and become more or less immovable.

General Lymphadenitis.—A general enlargement of all the lymph nodes of the body associated with fever and general symptoms of intoxication

occurs in both children and adults, but is more common in the former. The enlargement is more prominent in the cervical glands, but all of the regional lymph glands may be shotty and tender. Gastric disturbances and either constipation or diarrhœa may form a part of the clinical picture. In many of these cases there is no recognizable local infection, and the general picture is not that of any one of the known infectious diseases. Some of the cases belong to the class grouped under "glandular fever;" while others represent cases of "light measles," rubella, abortive scarlatina, influenza, etc. During influenza epidemics it is not an uncommon thing to see young children in houses containing adult cases develop fever and general glandular swelling without other symptoms. Such forms, as a rule, recover quickly, and suppuration rarely occurs.

A general adenitis may occur in any one of the acute infectious diseases, particularly in young children, and most frequently in scarlet fever, diphtheria, measles, rubella, chickenpox, etc. The condition not infrequently terminates in suppuration of some one of the regional groups, most commonly the cervical. Adenoids, chronic tonsillitis, chronic pharyngitis, etc., in young children are also occasionally associated with a universal enlargement of the lymph nodes. A similar chronic condition of the lymph glands is found also in rickets, congenital syphilis, acquired syphilis, lymphatic constitution, etc.

Cervical Lymphadenitis.—This is very common, particularly in children. It may be associated with any form of "*sore throat,*" and may occur as a complication in any one of the acute infections characterized by inflammation of the nose, tonsils, pharynx, larynx, etc. Infection through the gums, lip, face, scalp, alveolar abscesses, carious teeth, irritation of pediculi, eczematous conditions of the face, herpes, furuncles, etc., are among the conditions that may cause or be associated with enlargements of the cervical lymph nodes. In the mild cases the subparotid and the tonsillar lymph nodes alone may be swollen and tender. Suppuration not infrequently occurs in the severe forms of cervical lymphadenitis in children, but cervical abscesses are infrequent in adults, and when occurring are usually found in the submaxillary region and secondary to carious teeth. In young children the abscesses most frequently involve the subparotid nodes and are located beneath the deep cervical fascia and sternocleidomastoid muscle. "Pointing" takes place behind the upper margin of the muscle near the hair line, or anterior to the middle of the muscle on a level with the larynx.

"*Ludwig's angina*" may be in some cases a phlegmonous condition involving particularly the lymphatics and lymph nodes of the submaxillary region. The infection usually occurs through carious teeth or alveolar abscesses, and is usually due to the streptococcus. The process may become gangrenous, and is always severe. The prognosis is grave. Usually there is a sudden development of dyspnœa and dysphagia, with severe constitutional symptoms, followed by the formation of a tense phlegmon of the submaxillary region.

Abscesses in the lymph nodes of the *posterior cervical* or *occipital* regions may be caused by infection from furunculosis or pediculosis of

the scalp and neck. They are not as severe as those occurring anteriorly, are more superficial and heal more readily.

Retropharyngeal Abscess.—In the majority of cases this condition is due to an infection of the retropharyngeal lymph nodes, following scarlatina, influenza, rhinitis, pharyngitis, tonsillitis, etc. The majority of the cases occur during the first two years of life, since these lymph nodes atrophy after the third year. The abscess usually appears several days after the onset of the acute pharyngitis or rhinitis with which it is associated. Dyspnœa, dysphagia, difficulty in speaking, increase of fever, and general prostration mark the development of the condition. Of these symptoms the dyspnœa becomes the most marked and alarming, particularly in the case of infants. Examination of the posterior pharyngeal wall reveals the presence of a soft fluctuating swelling. This must be differentiated from the non-purulent swelling of the retropharyngeal lymph nodes found in association with large cervical abscesses. When the latter are opened externally, the retropharyngeal swelling disappears promptly. It is also important that the acute retropharyngeal abscesses be distinguished from *tuberculous abscesses* of this region due to tuberculosis of the cervical vertebræ. In the latter case the rigidity of the cervical spine, the character of the general symptoms, etc., will make the differential diagnosis an easy matter. Further, the acute pyogenic infections of the retropharyngeal nodes often give rise in young children to a clinical picture suggesting that of diphtheria. Local examination should settle the question, and there should be no particular difficulty when ordinary care is taken.

Chronic Cervical Lymphadenitis.—A chronic enlargement of the cervical lymph glands, more or less marked, is extremely common in school children. The subparotid nodes are usually affected, and it has been said that nearly all children attending public schools have palpable glands in this region. Such an enlargement is also common in young adults. The constant exposure of cases to infection of the respiratory tract is probably the chief cause of such chronic enlargements. The relationship between the two conditions is shown by the fact that in the majority of these cases the nodes are palpable or are distinctly enlarged only during the winter months, when respiratory infections are common, and that they subside during the warm season, when such infections are uncommon. Repeated infections in the same individual cause an increase in the size of the glands; and in such cases the nodes may remain permanently enlarged for several years. Interesting questions arise in this connection as to a possible etiological relationship between such chronic enlargement and the condition known as "status lymphaticus." Tuberculosis, Hodgkin's disease, lymphocytoma, and acute leukemia may develop on the basis of a previous chronic lymphadenitis. In some cases the enlargement follows one of the acute infections, particularly measles and scarlet fever.

The question of tuberculosis always arises in these cases of chronic lymphadenitis; and inasmuch as tuberculosis often does develop later in such enlarged nodes, a very careful differential diagnosis should be made. In some cases it is impossible to say whether the nodes are

tuberculous from the beginning or whether the infection with tubercle bacilli is secondary to a simple lymphadenitis, the latter condition lowering the resistance of the gland to the tubercle bacilli carried to it. The suspicion of the latter infection should always be entertained in every case of chronic hyperplasia of the lymph nodes, and the prognosis in such cases should be modified accordingly. Since an early diagnosis is of such great importance to the patient, every means should be taken to to fix the nature of the process as soon as possible. Tuberculin tests may be utilized, the opsonic index taken, or in doubtful cases the removal of one of the enlarged nodes and its careful microscopic examination should be insisted upon.

Lymphadenitis of the Axillary Glands.—Following infected wounds of the hands and arm there may develop a more or less marked inflammation of the axillary nodes. As a rule, the majority of these cases run a mild course, and even when large axillary abscesses are produced the general symptoms may be slight. The more serious cases are usually due to the streptococcus; but fortunately they are less common than the milder infections. The lymph nodes should be removed in these severe cases, but in the mild forms with little constitutional involvement the incision of the infected wound and free drainage usually result in a prompt resolution of the axillary swellings. The importance of infected "hang-nails" and cuts on the fingers in the production of ascending lymphangitis of the arm should always be borne in mind and should be carefully treated with the view of avoiding such sequelæ. Cryptogenic infection of the axillary nodes is not infrequent. Wounds of the fingers or hand received during postmortem examinations or septic surgical operations may sometimes be followed by rapid enlargement of the axillary nodes, with severe general symptoms, occasionally progressing in the course of a few hours to coma and finally death. Chronic lymphadenitis is almost always present in the axillary nodes in the case of mammary neoplasms, even when these are of a benign type. In the case of a malignant neoplasm of the breast a well-marked lymphadenitis of these nodes should be regarded as contributing to an unfavorable prognosis, even when no metastasis of carcinoma cells can be made out.

Lymphadenitis of the Bronchial Glands.—An acute simple inflammatory enlargement of the bronchial glands occurs in severe forms of bronchitis, pneumonia, and other acute inflammations of the lungs. It is very common in children in association with the acute infectious diseases, particularly when these are complicated with respiratory affections. It is highly probable that in the majority of cases of simple cervical adenitis there is at the same time more or less enlargement of the bronchial nodes. In the ordinary cases the symptoms due to the pressure of the enlarged glands cannot be separated from those of the primary condition; but when the enlargement is marked severe pressure symptoms may be produced. Dysphagia, dyspnœa, respiratory stridor, cyanosis, and the physical signs of bronchial stenosis constitute the clinical picture. Should suppuration occur, the abscess may rupture into the bronchi and sudden death ensue.

Lymphadenitis of the Mesenteric Glands.—Simple inflammations are of frequent occurrence in the mesenteric nodes. Severe gastritis, enteritis, peritonitis, appendicitis, omentitis, etc., are among the conditions primary to such enlargements. The enlarged glands are usually discovered at operation, but in some cases, when as large as small hickory-nuts, they may be felt through the abdominal wall, particularly in the appendix region, where they may be mistaken for encapsulated abscesses. Spontaneous resolution of such glands may occur.

Lymphadenitis of the Inguinal and Femoral Glands.—Aside from specific inflammations of the inguinal nodes, simple lymphadenitis is common as a sequel to wounds and inflammatory conditions of the feet or legs. Erysipelas, erythema, eczema, varicose ulcers, ulcus cruris, gangrene, etc., are some of the many conditions of the lower extremities characterized by swelling of the femoral and inguinal nodes. Infections of the external genitals are also a not infrequent cause of inguinal swellings. Direct trauma is also regarded by some as a cause of inguinal lymphadenitis. After excessive walking, running, jumping, etc., painful swellings of these nodes may appear. Resolution is usually speedy.

Lymphadenitis in the Acute Infections.—Measles.—In measles there is a more or less well-marked enlargement of all the lymph nodes of the body, particularly those of the posterior cervical, postauricular, and submaxillary groups. In severe cases the enlargement may be very pronounced. Resolution is often delayed, and a distinct chronic hyperplasia may persist. Suppuration is rare, and is usually secondary to some purulent complication of the upper respiratory or auditory tract. An increase in the size of the cervical glands after an attack of measles should always lead to a suspicion of tuberculosis.

Rubella.—This disease is characterized by a marked enlargement of the lymph nodes, usually to a greater extent than in measles. The cervical, submaxillary, postauricular, and occipital nodes may be as large as hickory-nuts, while the remaining regional lymph nodes are distinctly palpable, firm, and shotty. The lymphadenitis is usually coincident with the rash, sometimes preceding it by a few days, and gradually disappears. Suppuration is very rare, and the persistence of a chronic hyperplasia much less common than in measles.

Scarlet Fever.—A more or less pronounced general lymphadenitis is present in practically every case, but often is not noticed. The cervical glands are affected in proportion to the severity of the throat condition. They may be moderately enlarged, hard, and only slightly tender on pressure, or greatly enlarged, soft, and very painful. In the latter case suppuration may occur. This complication may develop early in the disease, or not until all other symptoms have disappeared. A tendency to a persistence of the lymphoid hyperplasia is often shown, and the question of a developing tuberculous lymphadenitis is of importance.

Diphtheria.—A lymphadenitis due to the action of the toxin is constantly seen in this disease, and is particularly marked in the severe and fatal cases. Since the cervical glands receive the toxins in the most concentrated form, they show the most marked changes. The enlarged

glands are hyperemic, soft, and homogenous on section. Hemorrhages and focal necroses occur in the germ centres and also in the lymphoid cords. In the severe cases of gangrenous scarlatinal diphtheritis the cervical nodes may present the microscopic picture of a gangrenous or necrotic hemorrhagic lymphadenitis. Chronic hyperplasia of the cervical nodes or of those of the entire body may be seen after diphtheria also, and tuberculosis may develop in such enlarged glands.

Chicken-pox.—Slight general enlargement of the lymph nodes is usually present during the onset but is usually so slight as not to be noticed unless the nodes are palpated. Chronic hyperplasia occurs more rarely after this affection than after the other infections of childhood.

Smallpox.—During the onset, the lymph nodes are always more or less swollen, this condition usually increasing until the height of the eruption, when it gradually subsides. On microscopic examination a marked sinus catarrh and œdema of the follicles are found. Great numbers of phagocytes are present in the sinuses. In severe cases hemorrhage may occur or a fibrinous exudate may take place into the sinuses. Streptococci are often present in the sinuses in large numbers. Usually no reaction occurs; rarely does suppuration take place. The writer has seen a case of generalized streptococcus, suppurative lymphadenitis during convalescence from smallpox.

Vaccinia.—The axillary glands on the side vaccinated are usually enlarged and tender on pressure. Such changes vary greatly in individual cases. They may be wholly unnoticed, or the patient may complain of a feeling of painful tension in the axilla. In cases with marked general reaction all of the regional lymph nodes may be more palpable than normal. Suppurative axillary lymphadenitis may follow secondary infection of the vaccine lesion.

Mumps.—Swelling of the cervical glands is common in severe cases of this disease. The inguinal glands may also be swollen and tender.

Influenza.—A polyadenitis of slight degree is very common in influenza. Swelling of the cervical glands is usually present in proportion to the severity of the throat condition. Children exposed to house epidemics may develop moderate fever with general glandular involvement.

Erysipelas.—Lymphadenitis of the lymphatic glands of the region affected often occurs. Suppuration is rare.

Pyemia and Septicemia.—A universal enlargement of the lymph nodes is very common. It may be slight or well marked.

Rheumatic Fever.—Rarely there is a universal polyadenitis of mild degree. The cervical glands may be tender and swollen when throat complications are present. When pericarditis occurs, the mediastinal glands are usually very much enlarged.

Anthrax.—The regional lymph glands of the part of the body in which the primary portal of infection is located show a marked hemorrhagic inflammation. Necrosis of the entire gland may result. In such inflamed glands great numbers of bacilli are present.

Glanders.—The lymph nodes are enlarged and show areas of round-cell infiltration. The regional glands of an area in which lymphangitis is present are greatly enlarged and painful. Suppuration may take

place. In chronic glanders a hyperplasia of the regional nodes may be seen.

Typhus Fever.—Some enlargement of the lymph nodes may be found in the early stages of this disease.

Typhoid Fever.—A general enlargement of the lymphatic glands is not uncommon as an expression of the lymphoid reaction to the toxins. It plays no part in the general symptomatology, and is usually unnoticed. Very rarely suppurative lymphadenitis occurs as a late complication or sequel.

Relapsing Fever.—During the onset an enlargement of the lymph nodes may be noted with the rapid increase in size of the spleen.

Epidemic Cerebrospinal Meningitis.—The glands may be slightly enlarged, soft, and hyperemic.

Pneumococcus Septicemia.—A general enlargement of the lymph nodes is usually present. Local infections due to the pneumococcus cause more or less regional lymphadenitis.

Infectious Jaundice.—Slight general lymphadenitis may be present.

Miliary Fever.—Slight general lymphadenitis.

Rocky Mountain Spotted Fever.—A more or less pronounced general enlargement of the lymph nodes.

Foot and Mouth Disease.—The submaxillary lymph nodes are usually enlarged and painful.

Glandular Fever.—This disease is characterized by a lymphadenitis of the cervical group usually, but sometimes of the axillary, inguinal, mediastinal, or mesenteric glands.

Malta Fever.—Slight enlargement of the mesenteric glands occurs.

Amœbic Dysentery.—The lymph nodes of the mesocolon are often enlarged, hyperemic, and œdematous. On microscopic examination they show a "sinus catarrh." Focal necroses and hemorrhages are rare.

Bacillary Dystentery.—The lymphoid tissue of the intestine, the mesenteric and retroperitoneal glands is hyperplastic and often hemorrhagic. Great numbers of bacilli may be found in the glands.

Malaria.—Swelling and pigmentation of the lymph nodes occurs in pernicious malaria. In chronic malaria the nodes may show the picture of a chronic lymphadenitis.

Trypanosomiasis.—A chronic polyadenitis is a constant feature of human trypanosomiasis, both the superficial and deep glands being involved, the latter usually to a greater degree. On microscopic examination the enlarged nodes show proliferation of the lymphoid tissue and stroma, hemorrhage, marked pigmentation, necrosis, etc. In the later stages the lymphoid tissue may be greatly reduced, the greater part of the gland consisting of newly formed, connective tissue. The lymph nodes may contain a greater amount of blood pigment than the spleen. Secondary pyogenic infection sometimes occurs and abscesses are formed in the enlarged nodes. Trypanosomes apparently occur in greater numbers in the lymph glands than in the blood or cerebrospinal fluid.

Bubo.—This term is sometimes used in a loose way to designate any marked inflammatory enlargement of a regional group of lymph nodes, but is more commonly and properly applied to the swellings of the

inguinal and femoral nodes occurring particularly in the venereal infections and in plague. It is also used to designate non-venereal inflammations of these glands resulting from infected wounds of the lower extremities of external genitals. The term is also applied to the glandular lesions of bubonic plague occurring in any region of the body.

Gonorrhœal Bubo.—The affected glands are painful and swollen, and these symptoms may persist for some time without change, resolution then occurring. The enlargement is usually moderate. Occasionally, particularly in cachectic individuals or as the result of other influences, such as trauma, etc., a secondary pyogenic infection takes place, suppuration occurs, and the course of the condition may be protracted. It is also probable that the gonococci alone may produce a suppurative lymphadenitis. In the non-suppurative gonococcal bubo the microscopic examination shows the presence of a simple lymphadenitis. Gonococci may be found in polynuclear cells in the lymph sinuses. The microscopic picture of the suppurative form possesses nothing distinctive from that due to other pyogenic infections.

In general the course and symptoms of gonorrhœal bubo resemble those of the bubo of soft chancre. The entire chain of glands from the anterior superior spine to the symphysis may be enlarged and the surrounding tissues so infiltrated that the individual nodes cannot be made out. In cachectic individuals the condition may be severe and protracted; in the majority of cases it runs a relatively mild course.

Chancroid.—Bubo is an extremely common complication of soft chancre, particularly in the male. It may develop at any time during the course of the soft chancre, or even after the latter has healed. When the lesion is located upon the genitals the inguinal nodes are affected; when located in other parts of the body corresponding regional nodes are involved. The afferent lymphatics may or may not be the seat of an ascending lymphangitis. Very often the nodes are involved without any signs of inflammation of the lymph vessels. The lymphadenitis develops acutely with severe pain, and often chills and fever, the affected glands frequently reaching the size of a small orange. There is considerable peri-adenitis, so that the entire group of nodes may appear as one solid mass. The swelling may occur on one side or on both. Usually the side affected corresponds to the seat of the lesion, but not infrequently the bubo may develop on the opposite side. The skin over the bubo is usually reddened and œdematous. The pain may be so severe as to interfere with the use of the legs. Within two or three weeks from the development of the bubo fluctuation may be felt and perforation through the skin usually follows. Resolution without suppuration is rare and takes place only in buboes of small size. With the advent of suppuration the pain usually diminishes in intensity, and may cease entirely with the rupture of the abscess. Repeated abscess formation may take place, or the entire chain may be converted into one large abscess. The latter event may often be prevented by early incision. Occasionally septicemia develops, leading to a fatal issue. Some buboes due to soft chancre run a very malignant course; destructive serpiginous ulcers may be formed, or the process may assume the character of a spreading gangrene.

In the majority of cases healing occurs after a more or less chronic course. Metastasis from the lymph nodes is usually stated never to occur. While recovery is often slow, the prognosis is good.

Syphilis.—The bubo of syphilis develops usually about four to five weeks after infection. The swelling of the inguinal glands is less acute, of slow development, and less painful than in the case of soft chancre. The glands alone are involved, the periglandular tissue usually remaining free. The enlarged nodes are rarely larger than a cherry; usually the entire chain of nodes is involved (syphilitic rosary). Both sides are usually affected, the nodes on the side on which the primary sore is situated being the larger. In uncomplicated cases suppuration does not occur, but in the case of mixed chancre an acute suppurative lymphadenitis may develop. The course of the pure syphilitic bubo is a very protracted one (*indolent bubo*). On microscopic examination the syphilitic bubo shows a lymphoid and endothelial proliferation, blocking of the sinuses with new endothelial cells and fibroblasts, loss of structural characteristics, and in the later stages a fibroid change. Spirochætæ may be demonstrated in the hyperplastic nodes. Collections of lymphocytes and plasma cells are found about the lymphatics and also the bloodvessels. Similar changes occur in the regional nodes of any part of the body in which the primary sore may be located. Resolution of the syphilitic bubo is attended by a fatty degeneration of the newly formed cellular elements. Atrophy and fibroid change usually follow.

Bubonic Plague.—The lymphatic nodes are specially involved in this disease, and the changes occurring in them form the chief features of the infection. The development of the bacillus apparently takes place more rapidly in the lymph nodes than elsewhere in the body. Periglandular œdema, infiltration, hemorrhagic necrosis of the lymphoid tissue and suppuration are the chief pathological features.

Treatment of Lymphadenitis.—The general indications in simple lymphadenitis are the removal of the infective agent, the prevention of suppuration, and the restoration of the glands to their normal condition. When suppuration has occurred the removal of the pus and the free drainage of the abscess are the chief therapeutic measures. The general condition of the patient demands special consideration. Rest of the affected region is important.

The proper management of the local infection usually brings about a prompt resolution of the lymphadenitis. In the cervical region the proper treatment of tonsillitis, pharyngitis, rhinitis, stomatitis, otitis, carious teeth, alveolar abscesses, furuncles, eczema, herpes, pediculi, etc., is the chief indication in those cases of lymphadenitis due to any one of these causes. Local treatment in the form of ice-bags, cold compresses, etc., is usually employed in an effort to increase the patient's comfort. Under such simple measures the adenitis associated with the acute infections usually disappears promptly in a large percentage of cases; and, in fact, such a resolution often occurs when no local treatment is given to the inflamed nodes. The use of iron, arsenic, and the iodides is still advocated as a therapeutic measure intended to raise the general strength and resisting power of the patient. All hygienic measures

having this aim should be employed according to the indications of the given case. Fresh air and proper feeding are more important than the administration of such drugs.

In the treatment of chronic lymphadenitis various external applications such as lead acetate, potassium iodide, lead iodide ointment, tincture of iodine, etc., are used locally to aid in resolution. The rôle played by these applications is a doubtful one, and they are to a certain extent falling out of use. Should they be employed, excessive irritation of the skin should be avoided.

In the treatment of bubo before suppuration has occurred, local applications of the tincture of iodine and belladonna, iodide of lead, lead acetate, etc., are much used in the form of moist dressings, ointments, plasters, etc. Injections into the bubo of benzoate of mercury, carbolic acid, mercuric chloride, silver nitrate, etc., are also advised, but the present tendency is toward less radical treatment. Rest in bed with warm applications, moist alcohol dressings covered tightly with rubber tissue or oiled silk, pressure bandages, etc., constitute the chief measures of treatment before suppuration takes place. Cauterization of the primary sore is regarded by some writers as favoring the development of bubo, the superficial crust formed increasing the growth of the infective agent and thus promoting the chances for involvement of the lymphatics and metastasis to the inguinal glands. After suppuration the treatment is surgical.

Tuberculosis.—This is, next to lymphadenitis, the most common affection of the lymph nodes. The peribronchial, mesenteric, and cervical groups are most frequently affected. The infection may be either hematogenous or lymphogenous, the latter being much the more common. In the majority of cases the tuberculous lesions in the lymph nodes are secondary to a primary focus in the region tributary to them; more rarely a primary cryptogenic infection of a node may occur. Three pathological varieties exist.

1. Miliary tubercles occur, either single or multiple. In the early stages they may be either *lymphoid* or *epithelioid*, usually the latter. Giant cells may or may not be present. Caseation occurs sooner or later. As the tubercles increase in size and number they may become confluent and gradually form large caseous masses. There is always an associated simple adenitis and peri-adenitis. Secondary infection and suppuration of the caseous areas often take place. Cyst-like spaces may thus be formed in the node, and perforation into a bronchus, the pleural or pericardial cavity, bloodvessel, lymph vessel, or through the skin may occur. A fistulous tract or an ulcer the sides of which are composed of tuberculous granulations may be thus formed. Streptococci are usually found in the pus. In other cases, after the death of the bacilli the caseous areas become inspissated or calcified, a dense connective-tissue capsule being formed about the mass. Secondary liquefaction of the caseous material leads to the formation of a cyst.

2. The affected node may present a *diffuse cellular hyperplasia*, either lymphoid or epithelioid in character, according to the age of the process. Giant cells may or may not be present. Caseation may be entirely

absent. The lymphoid tissue may become wholly replaced by epithelioid tissue, usually somewhat nodularly arranged, as if developing through the confluence of many foci. Few bacilli can be demonstrated on staining. The whole picture suggests an infection of low virulence. The affected nodes slowly enlarge, remain stationary sometimes for years, and gradually become hard and indurated. Contraction then follows. The development of connective tissue around the nodular centres of epithelioid proliferation often gives a granular appearance to the cut surface. The centres of the epithelioid foci may show a slight caseation. The cervical, axillary, cubital, and inguinal glands most frequently show this form of tuberculosis. Rarely all of the lymph nodes of the body may present such changes, the clinical picture being that of Hodgkin's disease.

3. The third form is characterized by a rapid caseation and softening, beginning either in one focus or in a number of foci scattered through the node. A node may quickly be completely caseated. On section the surface is smooth, dry, homogeneous, yellowish in color, and crumbling to the touch. Tubercle bacilli are present in large numbers, and the process is virulent in character. Epithelioid and giant cells may not be formed, and there may be no true tubercle formation, the caseation representing the primary destruction of the lymph node. The cervical, mesenteric, and bronchial nodes most frequently show this form of tuberculosis, and it is usually seen in children or cachectic individuals with low resistance. Secondary infection and suppuration may follow.

Combinations of two of these forms or of all three occur. There is no hard-and-fast line between them, nevertheless they occur sufficiently well-defined to constitute both clinical and pathological entities. Particularly is this the case with the diffuse cellular hyperplasia, the clinical picture being that of Hodgkin's disease or generalized lymphocytoma. The slowly caseating form (chronic tuberculous lymphadenitis) and the more rapid virulent form (acute tuberculous lymphadenitis) also constitute well-marked clinical entities.

Tubercle bacilli are constantly received by the lymph nodes and destroyed by them, in the great majority of cases without the production of any perceptible lesion. It is, of course, well known that positive results may be obtained by the inoculation of lymph nodes showing no tuberculous changes. In other cases minute focal necroses may be formed before the bacilli are killed off or are inhibited in their growth. The spontaneous healing of small tubercles is also of frequent occurrence. The site of such healed lesions is usually shown by the formation of a hyaline mass. It is the writer's belief that the small hyaline areas so common in lymph nodes, particularly in those of the mesenteric and retroperitoneal regions, represent in the majority, if not in all cases, small healed tuberculous lesions.

The presence in the body of lesions containing virulent tubercle bacilli is a constant menace. Rupture of the caseous area into a lymph vessel, thoracic duct, or vein may give rise to a generalized miliary tuberculosis. Likewise, the occurrence of tuberculous meningitis as a sequel to tuberculous lymphadenitis is not uncommon. In cases of tuberculosis of

the bronchial glands occurring in children, a simple bronchopneumonia due to measles or scarlet fever may become converted into a widespread caseous pneumonia. The possibilities of such sequelæ make tuberculosis of the lymph nodes a very grave affection, particularly in children.

The cervical, bronchial, and mesenteric lymph nodes are most often the seat of tuberculosis. In the case of the *cervical glands* the submaxillary nodes are more frequently involved. The infection may reach the glands through the mucosa of the upper respiratory tract without the occurrence of local lesions; or the tuberculous lymphadenitis may be secondary to a tuberculosis of the tonsils, adenoids, nose, pharynx, middle ear, skin, etc. Carious teeth may form an avenue of entrance for the bacilli. The nodes may enlarge slowly or an acute enlargement may take place. A nodular mass may be formed along the jugular vein. For months or even for several years the condition may show no change, although there is usually a tendency toward a progressive involvement of a number of nodes. Suppuration and perforation of the skin occur very frequently. The majority of the patients appear for treatment during the latter part of the winter and early spring.

Tuberculosis of the *bronchial nodes* may be primary, the bacilli either passing the lungs without exciting lesions there, or they are brought to the nodes through the thoracic duct. Secondary involvement occurs in tuberculosis of the lungs, cervical nodes, vertebræ, ribs, sternum, clavicle, mammary gland, etc. Some writers hold that the entrance of tubercle bacilli into the lymph in any part of the body may cause tuberculosis of the bronchial nodes. Bacilli taken through the intestinal mucosa without producing any lesion in it may be carried through the thoracic duct and through the lungs to excite first in the bronchial nodes the characteristic lesions of tuberculosis. The affected nodes may be large or small, hard or soft, indurated or calcified. Large caseous masses may be formed. *Pressure* upon the trachea or bronchi may give rise to a respiratory stridor; while compression of the heart or great vessels may cause circulatory disturbances. Dyspnœa, stridor, asthma-like attacks, hoarseness, cough, cyanosis, dysphagia, vomiting, paralysis of vocal cords, inequality of pupils, etc., are the chief clinical symptoms. The sternum may be arched forward. Severe pain is often felt in the region of the upper dorsal vertebræ. An area of dulness may be obtained by percussion, and the *x*-ray picture may show definite shadows corresponding to the diseased nodes. Loud venous murmurs may be heard on auscultation. These are probably due to the pressure upon the left innominate vein. Perforation may take place into the bronchi, lungs, pleura, pericardium, trachea, œsophagus, or large vessels. Aspiration tuberculosis, usually in the form of a caseous pneumonia, may be produced in the lungs, or a general miliary tuberculosis or tuberculous meningitis may form the final phase of these cases.

Infection of the *mesenteric nodes* may take place from bacilli that pass the intestinal mucosa without exciting any lesion there; or it may be secondary to tuberculous lesions of the intestine or of any part of the body tributary to the thoracic duct. The bacilli may be either the *bovine* or the *human* strain. The former is found chiefly in infants as the result

of the ingestion of milk from tuberculous cows. Infection with the human strain is usually the result of auto-infection of the intestine from bacilli swallowed in the sputum. Bacilli taken in with dust and swallowed with the saliva may also give rise to mesenteric tuberculosis. In the opinion of the writer healed tuberculosis of the mesenteric and retroperitoneal nodes is of very frequent occurrence. In the great majority of adult cadavers small hyaline areas may be found in these nodes. An extensive study of these has led the writer to believe that the majority, if not all, of such hyaline deposits represent healed tuberculous lesions. The entrance of tubercle bacilli into the mesenteric and retroperitoneal nodes must then be of very frequent occurrence, and the importance of the intestinal route of infection must be emphasized. The early healing of such lesions indicates an infection with a strain of low virulence, possibly the bovine form. As a distinct clinical entity, tuberculosis of the mesenteric nodes is not nearly so common as that of the cervical nodes. It occurs as such chiefly in children under the clinical picture of *tabes mesenterica*. In this affection the mesenteric nodes may become converted into large nodular caseous masses. Absorption from the intestine is greatly diminished. The child becomes greatly emaciated, the abdomen is distended, and an insatiable appetite, diarrhœa, and offensive stools are the chief symptoms. A fatal termination is inevitable. Only rarely does tuberculosis of the mesenteric nodes occur in such a localized form that surgical removal is possible.

Tuberculosis of the *axillary nodes* is not rare, and is usually associated with tuberculosis of the arm or mammary gland; tuberculous warts received through autopsy or surgical operation may be the source of the bacilli carried to the lymph nodes. The *epitrochlear gland* is usually involved also, or may alone be affected.

The *inguinal nodes* are also not infrequently the seat of a tuberculous infection. Tuberculous ulcers of the foot following wounds are the most common sources of the infection, but it may be associated with tuberculosis of the external genitals. The involvement of the lymph nodes may be rapid or slow, and the course virulent or very mild.

Generalized tuberculous lymphadenitis is relatively rare. The condition is very chronic, slowly progressive, and presents a clinical picture that often cannot be differentiated from that of Hodgkin's disease except by a microscopic examination of one of the affected nodes. The microscopic features are wholly distinct from those of true Hodgkin's disease.

Differential Diagnosis.—The diagnosis of a tuberculous lymphadenitis is often very difficult or wholly impossible without a microscopic examination. In the early stages it is very difficult to distinguish between simple hyperplastic lymphadenitis and tuberculosis. Persistence for several months of the glandular enlargement, a swelling of the gland to the size of a hickory nut, a beginning softening, etc., are the chief indications of tuberculosis. Since it is important that the diagnosis should be made early, the excision of a node for microscopic examination should be insisted upon. In the case of the enlargement of the nodes of a given region or of the entire body, the differential diagnosis will depend upon the microscopic examination of an excised node. The clinical differ-

entiation usually given cannot be depended upon. A tuberculin test may also be used in doubtful cases.

Treatment.—The general treatment for tuberculous lymphadenitis is that for tuberculosis in any part of the body. Rest, fresh air, and abundant and proper feeding are the chief means of increasing the patient's general resistance. Under such hygienic measures some patients greatly improve, and healing of the tuberculous process may take place. The internal use of potassium iodide, iron, and arsenic is still regarded by some practitioners as of great value. Counterirritation, injections of iodine, mercury, carbolic acid, etc., incision and drainage, etc., are still used in the treatment of softened nodes. By the best representatives of the modern school such methods are regarded as bad, and but one thing is advised—the early removal of the affected nodes. All cases, therefore, should be regarded as surgical as soon as the suspicion of tuberculous lymphadenitis becomes well founded. A large incision should be made, and the entire group containing the affected nodes should be cleaned out. It is unwise to remove only those nodes that are apparently enlarged. Recurrence practically always takes place after such incomplete operations. The proximity of the nodes underneath the sternocleidomastoid to the spinal accessory nerve and internal jugular vein make their removal a matter of careful work. The scar resulting from a good operation is very slight, and is not to be compared with the disfigurement resulting from spontaneous perforation. The latter event should never be allowed to occur. After the operation the patient should be treated for some time along antituberculosis lines.

The use of the Röntgen rays is not advised for the treatment of tuberculous lymph nodes. Too many dangers attend the prolonged and vigorous irradiation necessary to reduce the size of enlarged nodes. Moreover, in glands so treated an active eruption of miliary tubercles may occur at the periphery of the caseous areas. Tuberculin, the vaccine method, etc., may be also employed. In the rare cases of general tuberculous lymphadenitis these are about the only therapeutic measures offering any hope of delaying the course of the disease. Surgical removal of all the regional lymph nodes is not possible, but the groups showing the greatest involvement may be removed and specific antituberculosis treatment carried out.

Scrofula.—Modern medicine does not recognize a distinct clinical entity under the term "scrofula" or "scrofulous." The clinical complex of chronic hyperplasia of the cervical, bronchial, and mesenteric lymph nodes, leading sooner or later to caseation, associated with tuberculous processes in the bones and joints, chronic inflammations of the mucous membranes of the eyes, ears, nose, pharynx, swollen lips, "scrofulous habitus," etc., is regarded only as a special form of tuberculosis.

Syphilis.—Aside from the bubo attending the primary lesion, constitutional syphilis is associated with two distinct forms of changes in the lymph nodes, cellular hyperplasia, and gumma. In the first the nodes are moderately enlarged, hard, homogenous, and grayish on section. The glands in any part of the body may be affected, particularly the inguinal, cervical, occipital, pectoral, and cubital nodes. These may

become affected in the primary or early in the secondary stage, and this may persist for years, the nodes finally becoming atrophic and indurated. In the later stages the lymphoid tissue becomes atrophic and the nodes may come to consist wholly or chiefly of dense, hyaline, connective tissue. Gummata are found but rarely in the lymph nodes, and are practically always located in the regional lymph nodes of an organ containing gummata. In cases of gummata of the liver the nodes at the portal fissure may contain gummata, while in gummata of the skin or muscles the corresponding nodes may be similarly affected. Suppuration is less common in syphilitic nodes than in tuberculous, but abscesses are sometimes formed. The diagnosis is usually easy from the history and associated lesions. Small nodules of epithelioid cells resembling tubercles are often found in the lymph nodes of tertiary syphilis. They represent miliary gummata. Giant cells are usually not present, but may be; and the diagnosis is usually difficult for the non-expert. This is probably one of the most frequently mistaken conditions in pathological diagnosis. The vascular proliferation with the association of endarteritis and endophlebitis obliterans are important diagnostic points. The treatment is along antisyphilitic lines.

Leprosy.—In leprosy the lymph nodes of an affected region or throughout the entire body may be enlarged, firm, and yellowish-white on section. Microscopically, a condition of cellular hyperplasia is present and lepra bacilli may be demonstrated in the lymphoid tissue.

Retrograde Changes.—Simple atrophy, with or without *fatty infiltration,* occurs in old age and in general obesity, anemia, cachexia, etc. The node may be completely changed into a kidney-shaped fat lobule having a thick capsule; or fat cells may occur in numbers throughout the lymphoid tissue. *Fatty degeneration* occurs in the lymphoid cells after Röntgen irradiation, resolution of glandular hyperplasias, buboes, etc. *Amyloid* may occur in association with general amyloidosis, or as a local change following syphilitic inflammation, etc. It is found also in lymphomata, indurated nodes of Hodgkin's disease, etc. *Hyaline degeneration* is very common in chronic lymphadenitis, tuberculosis, secondary carcinoma, Hodgkin's disease, etc. The great majority of the localized hyaline areas in lymph nodes represent, in the writer's opinion, healed tuberculous lesions, particularly in the mesenteric and retroperitoneal nodes. *Calcification* is very common in old tuberculous lesions, necrotic areas, hyaline deposits, old abscesses, secondary tumors, etc. True *bone* may be formed in old calcified tubercles. *Caseous necrosis* of the lymphoid tissue may be produced by Röntgen irradiation, action of many pathogenic bacteria, etc.

Pigmentation of the lymph nodes occurs through deposits of carbon dust (anthracosis), blood pigment (hemosiderosis), pigments used in tattoo, bile pigment (icterus), and melanin (Addison's disease, melanotic sarcoma, etc.). In stone-cutters and iron-workers deposits of dust in the bronchial nodes leads to induration of these glands. The nodes may be enlarged, hard, and indurated, or soft and friable. Fatty degeneration and caseation or liquefaction necrosis may occur when the amount of pigment is large. Rupture of a softened node into the blood stream

leads to a general metastasis of the pigment (anthracotic softening). In the great majority of cases such perforations are due to an associated tuberculosis of the pigmented node. Miliary tuberculosis often follows such a pigment metastasis. After splenectomy a deposit of iron-pigment (hemosiderin) is found in both lymph and hemal nodes, particularly of the retroperitoneal region.

Secondary Neoplasms.—Secondary *sarcoma* occurs frequently in the lymph nodes, metastases even of the harder forms, such as osteosarcoma, not infrequently being found in the regional nodes. In the case of softer and more malignant forms, such as round-cell melanotic sarcomata, the regional nodes usually become involved very early. *Endotheliomata*, particularly those of the serous membranes, may also give rise to secondaries in the lymph nodes. *Secondary carcinoma* occurs in the lymph nodes with much greater frequency than secondary sarcoma. In all of its various forms carcinoma shows a special tedency to invade the lymphatics and give rise to metastases in the regional nodes. Usually the secondary growth has a structure like that of the primary, but it sometimes shows a very different one. The young metastases are richer in cells, soft, and possess relatively little stroma. For this reason the malignant nature of a scirrhus carcinoma can usually be best made out in the metastases found in the lymph nodes.

The symptoms of the secondary development of tumors in lymph nodes are the progressive enlargement of the regional nodes, periglandular infiltration, secondary degeneration, lymph stasis, etc. It must be remembered, however, that nodes apparently not enlarged may have their elements wholly replaced by tumor tissue. In other cases the metastatic growth may exceed the primary in size. The consistence may be hard or soft; the cut surface is usually whitish, sometimes mottled. On scraping, an abundant cell juice can be obtained from cellular tumors. The differential diagnosis rests wholly upon the microscopic findings. The regional lymph nodes of any organ the seat of a malignant neoplasm practically always show a chronic lymphadenitis, and an enlargement of the nodes may be due to this when no metastases are present. The treatment of metastatic tumors of the lymph nodes is wholly surgical. In inoperable cases Röntgen irradiation may be used to check the growth and prevent further metastases.

Secondary Leukemic Change.—The lymph nodes may be involved secondarily in either lymphemia or myelemia of bone-marrow origin. In chloroma, likewise, the nodes show secondary changes. The enlargement may be slight, or large nodular tumors may be produced in the regional groups. In leukemic myelosis usually certain groups (retroperitoneal especially) are involved. The myeloid changes are always most marked in the medullary portion of the nodes. Aleukemic myelosis of the lymph nodes has not yet been seen reported, although Aschoff has observed heteroplastic myeloid changes in a node. Röntgen irradiation and the administration of arsenic constitute our only effectual therapeutic measures.

PRIMARY AFFECTIONS OF THE LYMPH NODES.

These consist almost wholly of progressive hyperplasias and tumor-like formations, the etiology and nature of which are not clear. They practically all run a malignant course, leading sooner or later to death. Compared with the secondary affections of the lymph nodes they are relatively rare, but are by no means infrequent. In the literature they appear under a great variety of designations, and a satisfactory classification of the reported cases is impossible. According to the writer's belief, the majority of the conditions are genetically related and show transition phases. This is particularly true of the leukemic and aleukemic lymphocytomata (lymphomata, lymphosarcomata).

Lymphocytoma.—The hyperplastic and neoplasm-like conditions of the lymph nodes depending upon an overgrowth of cells of the type of lymphocytes, either of the small variety or the large, are here brought into one general class, the *lymphocytomata.* This includes all the lymphocytomatous tumors classed variously as lymphoma, lymphadenoma, lymphosarcoma, pseudoleukemia, adenia, lymphadenomatosis, lymphomatosis, etc. In all of these conditions the essential thing is an *overgrowth of lymphocytes* occurring primarily in preëxisting lymphoid tissue. All stages of transition exist between glands in which there is a simple lymphoid hyperplasia and tumors the cells of which infiltrate the capsules of the nodes and invade the neighboring tissues. The former are usually classed as benign lymphoma, lymphadenoma, pseudoleukemia, etc., while the more malignant infiltrating varieties are grouped under the head of lymphosarcoma. In all cases cells of the lymphocyte type constitute the essential tumor element, and for that reason all the forms, including all the transition varieties between one extreme and the other, may be conveniently grouped under the head of lymphocytoma. From the ordinary forms of sarcoma the lymphocytomata are distinguished by the fact that the latter spread progressively through the lymphatic system and do not set up hematogenous metastases. The writer believes that all of these lymphoid hyperplasias are genetically related. They may be divided into two great groups, *leukemic* and *aleukemic,* according to the blood condition. So far as the essential pathology is concerned, no histological difference can be discovered between these two types, and one may pass into the other. A further classification is that of *generalized* and *localized* or *regional lymphocytoma.* According to the slowness or rapidity of the course a clinical classification into *benign* or *malignant* lymphocytoma may also be made, but in all cases the process is a progressive one, although the course at times may be very slow.

Generalized Aleukemic Lymphocytoma.—All of the lymph nodes may at the same time or in succession show a progressive enlargement. Large nodular masses may be formed in the cervical, axillary, etc., regions. The individual nodes may be felt, or they may be fused together. The consistence may be firm or soft. Fluctuation may occur. The nodes may or may not be adherent to the overlying skin. Spontaneous resolution of enlarged nodes may occur at times. The general condition may remain good, or fever, tendency to hemorrhage, inflammations, etc.

may develop. In some cases the patients rapidly become emaciated and quickly die. Pressure from the enlarged nodes may cause œdema, ascites, chylous ascites, chylothorax, compression of the trachea, suffocation, etc. Cases that have run a benign course for many years may suddenly become malignant in character or may develop leukemia. In the malignant forms the tissue about the nodes becomes infiltrated, the liver, lungs, kidneys, bone-marrow, and all the serous surfaces may show infiltrations or nodular metastases. In the so-called benign forms similar infiltrations and lymphomata are found in the internal organs, particularly in the liver. The growth of the tumors may be very rapid, and extensive areas of degeneration and necrosis may be found in them. Perforation and ulceration may occur. Microscopically the rapidly growing forms show a more atypical structure than the benign forms. According to the development of the stroma *hard* and *soft* forms may be produced.

Fig. 56

Lymphocytoma of parotid gland. From a case showing xerostomia as the chief clinical feature.

Regional Lymphocytoma.—This form differs from the above only in the fact that the tumor-like growths develop in certain regions, while the other lymph nodes of the body show a much less degree of involvement, often being only moderately enlarged. The course of the disease is a progressive one, and aside from the changes due to the local tumors,

the pathological picture is essentially the same as that seen in the generalized form. The following varieties may be distinguished:

1. Symmetrical enlargement of lacrimal or salivary glands. Failure of lacrimation and xerostomia are the special symptoms dependent upon the local enlargements. (See Fig. 56.)

2. Mediastinal lymphocytoma with pressure symptoms as the most important clinical features.

FIG. 57

Lymphocytoma of the intestine.

3. Lymphocytoma of stomach or intestine and mesenteric glands. The chief symptoms are abdominal tumor, achylia, diarrhœa, ascites (chylous), chylothorax, œdema of lower extremities, etc. In the writer's experience this has been one of the most common forms. Four cases of this type occurred in his pathological material in two years. (See Fig. 57 and Plate XV.)

4. Retroperitoneal lymphocytoma, with symptoms similar to preceding.

5. Cervical or axillary lymphocytoma, often unilateral.

6. Lymphocytoma of the pharynx.

7. Lymphocytoma of the skin (mycosis fungoides).

These are the most common and striking clinical varieties, but any region (rectum, testicles, etc.) may be the seat of the chief growth. The remaining lymph nodes may show a moderate enlargement; miliary lymphoid nodules may be found in the lungs, liver, kidneys, spleen,

PLATE XV

Lymphocytoma of the Ileum and Mesenteric Glands.

adrenals, parotid, bone-marrow, omentum, etc., while the spleen, as a rule, is not greatly enlarged or not at all. The writer has seen lymphatic leukemia develop in three cases of the intestinal type, in two cases of symmetrical enlargement of the lacrimal glands, and in one case of pharyngeal and cervical localization.

Diagnosis.—This rests chiefly upon the microscopic examination of one of the enlarged nodes, excised for this purpose.

Treatment.—Both the *generalized* and the *regional* forms of lymphocytoma are incurable. The benign forms run a slow course, often into old age, while the duration of the malignant type is usually two to three years. Cases running a benign course at first may later take on a malignant character. The internal use of arsenic and the careful use of Röntgen irradiation may serve to delay the fatal termination. Although the tumors may be greatly reduced by such treatment, symptoms of intoxication may arise and the patient die while it is being carried out. The surgical treatment may give prolonged relief in the case of the slowly growing forms, but operation is always followed by recurrence in the case of the more malignant type and often in the benign. No matter how thoroughly a region may be freed of the growths, enormous tumors may again develop within it during a relatively brief space of time.

Hodgkin's Disease.—Although this subject is discussed elsewhere it is proper here to call attention to the variety of pathological conditions found in cases corresponding clinically to the classical symptom complex of this affection. By many writers the forms of lymphocytoma described above are regarded as Hodgkin's disease or pseudoleukemia. Other writers (Reed, Longcope, MacCallum, etc.) regard as the essential histological changes of Hodgkin's disease a process very different from that of lymphoma or lymphosarcoma, and which is characterized by changes resembling a chronic inflammatory process, consisting of proliferations of endothelial and reticular cells, formation of giant cells, presence of many eosinophiles, and a progressive fibrosis. The writer agrees that such a distinct pathological condition exists. He has found it in about a third of his pathological cases diagnosed clinically as Hodgkin's disease. Of the other cases, the majority showed a histological picture of lymphocytoma, two cases presented the picture of a diffuse epithelioid tuberculosis without caseation, one case showed myeloid changes in the nodes, and another the picture of a hemangio-sarcoma. At the present time it would appear much better to limit the pathological diagnosis of Hodgkin's disease to the chronic inflammatory type of Reed, Longcope, etc., until its etiological nature is discovered. It is convenient to speak of it as the *endothelioid* type of Hodgkin's disease. The infective nature of Hodgkin's disease is being strongly urged at the present time, and the tendency is to consider it as one of the infective granulomas (*Hodgkin's granuloma*). Several observers have independently during the last year isolated bacilli of a diphtheroid type from the enlarged nodes of Hodgkin's disease, and a vaccine therapy based upon these findings is now in the experimental stage.

Leukemia.—In lymphatic leukemia the lymph nodes may be primarily involved. Single nodes, single groups, or all of the lymph glands of

the body may become enormously enlarged, as the result of an active hyperplasia of the lymphoid elements. The microscopic picture cannot, aside from the great numbers of white cells in the blood, be distinguished from that of lymphocytoma. The same nodular or diffuse formation of atypical lymphoid tissue takes place in the liver, lungs, kidneys, spleen, bone-marrow, etc. The clinical features of leukemic lymphocytoma are usually those of a more malignant condition than the aleukemic form. The spleen is usually greatly enlarged, there is often a marked tendency to hemorrhage, there is greater prostration, and the cases usually run a more rapid course. A fatal termination may be reached within limits varying from a few months to two or three years. Under careful treatment with arsenic and Röntgen irradiation the fatal event may be postponed, in some cases for a year or two.

It is a question as to whether myeloid changes occur primarily in the lymph nodes. A few cases suggesting this have been observed, and the writer has reported a remarkable case originally showing the clinical and pathological features of an endothelioid Hodgkin's. Two years after the operative removal of the enlarged cervical nodes, recurrence took place and while under treatment with Röntgen irradiation a lymphatic leukemia gradually developed. The study of the nodes, spleen, bone marrow, liver infiltrations, nodules, etc., showed throughout the picture of a myeloid change ("myeloid sarcoma"). It is impossible at the present time properly to classify such a condition.

Lymphatic Constitution.—The condition of lymphatic constitution or lymphatism (status lymphaticus) is discussed under diseases of the thymus. In the early stages of this affection there may be found in the thymus, lymph nodes, spleen, and bone-marrow a condition of lymphoid hyperplasia somewhat like that of aleukemic lymphocytoma. In the later stages the lymph nodes and spleen may be atrophic, and the proliferations of endothelium and reticulum may give a picture suggesting that of the endothelioid type of Hodgkin's disease. Indeed, it cannot be said at the present time that such cases are not on the border line between conditions of chronic inflammatory hyperplasia and Hodgkin's disease or lymphocytoma. In the case of the so-called lymphatic constitution it is very probable that no definite pathological and etiological entity exists, but that it represents the various stages of reaction to a chronic lymphoid or myeloid intoxication having a varied etiology and pathology. The hyperplasia of the thymus becomes the feature of chief interest, and this may be regarded as an essential feature of the lymphoid hyperplasia or as of the nature of a compensatory hypertrophy.

Primary Neoplasms.—Aside from the various forms of lymphocytoma, primary tumors of the lymph nodes are rare. They differ from the former in that they arise in single nodes, quickly break through the capsule, and invade the surrounding tissues. The neighboring lymph nodes are affected only through direct involvement. Metastasis is hematogenous and not through the lymphatics. Round-cell and spindle-cell fibrosarcoma, angiosarcoma, and endothelioma have been observed. The alveolar endotheliomata are often mistaken for carcinoma, and have been regarded by some writers as primary lymph-node carcinomata.

The writer has seen a case of generalized angiosarcoma of the lymph nodes resembling in all respects clinically Hodgkin's disease.

Cysts of the lymph nodes arise through the dilatation of the lymph sinuses with secondary atrophy of the lymphoid tissue. Many of the mesenteric cysts arise in this way, and the writer has seen cases in which the mesentery was studded with cysts, each one arising in a lymph node. Papillary cystadenomas have been reported as occurring primarily in lymph nodes. Such growths must be teratoid in origin.

In the cervical region branchial cysts are often found completely surrounded by lymphoid tissue. Not infrequently such nodes are removed under the impression that they are tuberculous.

Metastatic sarcoma is rare in lymph nodes, except in the case of melanotic sarcoma, when the regional lymph nodes always show metastases. The great majority of secondary lymph node neoplasms are carcinomatous.

Parasites.—Trichina embryos may be found in the lymph sinuses of the mesenteric lymph nodes during the period of invasion.

HEMOLYMPH NODES.

The general pathology of the hemolymph nodes is essentially the same as that of the lymphatic glands. Of their special pathology but little is known.

Pernicious Anemia.—In the majority of cases of this disease the hemolymph nodes of the prevertebral region are hyperplastic, very red or brown in color, and often increased in number. On microscopic examination the chief feature is the great increase in the number of red cell destroying phagocytes in the blood sinuses, and the large amount of blood pigment present. The number of phagocytes containing blood pigment may exceed that in the spleen, liver, or bone-marrow. Great numbers of mononuclear eosinophiles may be present. In certain forms of pernicious anemia the hemolymph nodes must be regarded as a seat of excessive hemolytic action.

Posthemorrhagic Anemia.—In a fatal case of epistaxis due to a hemangiomatous polyp the prevertebral hemolymph nodes showed myeloid changes.

Banti's Disease.—In four cases of splenic anemia with early and late stages of hepatic cirrhosis the prevertebral hemolymph nodes showed marked hyperplasia and excessive destruction of red cells. A distinct new formation of hemolymph nodes was seen in the prevertebral and mesenteric fat tissue.

Leukemia.—In many case of leukemia the prevertebral hemolymph nodes show more marked changes than do the ordinary lymphatic nodes. Lymphoid and myeloid metaplasias and hyperplasias occur, and the earlier involvement of the hemolymph nodes points to some special relationship in function to that of the bone-marrow.

Pseudomelanosis.—Pseudomelanosis of the hemolymph nodes has been observed by the writer in a number of cases of generalized infection with

the colon bacillus. Only the hemolymph nodes presented the change, the deep black color being due to a union of the hydrogen sulphide contained in the blood and tissues with the hemosiderin of these nodes.

Reaction to Infection.—In all infections characterized by a general intoxication the hemolymph nodes show a marked reaction. This is particularly the case in streptococcus infections. Marked proliferation of the endothelium of the blood sinuses occurs, and there is greatly increased phagocytosis. The amount of hemosiderin contained in the nodes may be so great as to give them a deep chocolate-brown color. The neighboring lymphatic nodes in such cases may be devoid, or nearly so, of pigment. Hyperplasia of the hemolymph nodes occurs in sleeping sickness and in chronic malaria.

These findings go far to show that the hemolymph nodes have a function distinct from that of the ordinary lymph nodes, and that it is in some special way concerned with blood destruction and hematopoiesis, and also most probably with the processes of protection and immunity. The determination of the exact nature of this function must be left to the future.

Mercuric Chloride Poisoning.—In a fatal case of poisoning with mercuric chloride, the retroperitoneal hemolymph nodes were much enlarged and deep red in color, and showed multiple thromboses of agglutinated red blood cells in the sinuses. The lymph nodes showed no changes.

CHAPTER XIX.

HODGKIN'S DISEASE.

By WARFIELD T. LONGCOPE, M.D.

Definition.—Hodgkin's disease is an affection characterized by painless progressive enlargement usually of several groups of lymph nodes and accompanied by a progressive anemia. Often the spleen, and sometimes the liver, is enlarged.

Etiology.—Distribution.—Hodgkin's disease seems to be widely distributed over the countries of Europe and through America, and may exist in all parts of the globe, although, owing to the lack of reports from certain countries, this fact is difficult to ascertain. In America the reported cases have occurred with few exceptions in whites. The disease is said to affect dogs, horses, and pigs, but a more accurate and extensive study is necessary before one can assert that these glandular swellings in animals are the same as Hodgkin's disease in man.

Sex.—The disease is much more common in men than in women. Of the 100 cases which Gowers collected, 75 were in males, 25 in females; of the 102 cases which Fischer collected, 86 were in males, 38 in females; of Ziegler's[1] 220 collected cases, 149 were in males, 71 in females; and of the 86 cases which the writer has collected, 58 were males and 28 females.

Age.—Young adults are especially susceptible, although the affection has been described in extreme youth and old age: 34 per cent. of Gowers' cases occurred between the ages of ten and thirty; 74 per cent. of Fischer's cases occurred between the ages of fifteen and thirty-five. In the writer's series the cases occurred in the various decades as follows:

Years.	Cases.
Before 10	17
10 to 20	23
20 to 30	15
30 to 40	17
40 to 50	5
50 to 60	5
60 to 70	2
No age given	2
Total	86

Predisposing Causes.—Various factors have been suggested as predisposing causes, and of these the one most frequently mentioned is local inflammation. By certain authors a good deal of stress has been laid especially upon inflammations of the throat and also of the eyes, ears, nose, and teeth. Since the disease usually starts in the cervical lymph

[1] *Die Hodgkinsche Krankheit*, 1911.

glands, it is natural that infection of the throat and tonsils should be looked upon with favor as a predisposing factor. Local irritation has been mentioned as a possible factor. Heredity is probably unimportant, and a history of syphilis can be obtained in comparatively few cases. There is no evidence to show that the disease can be transmitted from one person to another, although in a few instances a history of glandular swellings in other members of the family has been obtained.

Nature of the Disease.—For many years the disease was thought to be a true tumor and though this question is still discussed, the prevailing view of both continental and American investigators, and the one for which there is most support, is that the swellings are of the nature of granulomata and represent a chronic inflammatory process.

The etiology is not definitely determined. Up to the present time attempts to transmit the disease to guinea-pigs, rabbits, dogs, and monkeys have not been successful. With the appearance of Sternberg's papers the old question as to the tuberculous origin of Hodgkin's disease was revived and since then the problem has been much discussed. The matter has been complicated by the frequent occurrence of undoubted tuberculosis with Hodgkin's disease, and while one group of observers maintains that tuberculosis is in no way the cause but occurs only as a secondary infection, another group follows Sternberg and holds that Hodgkin's disease is in reality a modified form of tuberculosis and due to the tubercle bacillus. The failure, however, in long series of cases to demonstrate tubercle bacilli either in sections of the glands or through animal inoculations, must preclude the idea that the disease is caused by it.

The other older bacteriological studies gave irregular or wholly contradictory results, but recently much attention has been paid to the findings of Much and Fäenkel,[1] who have described Gram positive granular bacilli in the material from glands treated with antiformin. Much's observation has been repeatedly though not regularly confirmed, and recently Kusunoki[2] has seen the bacilli not only in material treated with antiformin but in sections from sixteen cases.

The exact relationship which the rod-like bodies bear to the disease is not as yet clear, though they are considered by some to be the cause. More recently de Negri and Mieremet,[3] and Bunting and Yates[4] independently in this country, have obtained cultures of a Gram positive diphtheroid bacillus from the glands of cases of Hodgkin's disease. Their results have been confirmed by Rosenow.[5] According to Bunting and Yates, who believe that this diphtheroid bacillus is the cause of Hodgkin's disease, inoculations of pure cultures into monkeys give rise to a local enlargement of lymph nodes which reproduce in their histological appearance the pathological picture of the disease in the human individual.

Pathology.—Lymph Glands.—The anatomical picture which this disease presents at autopsy is often one of a striking character. If the glandular

[1] *Münch. med. Woch.*, 1910, lvii, Nr. 13. [2] *Virchows Arch.*, 1914, ccxv, 184.
[3] *Centralbl. f. Bakt. u. Parasitol.*, Orig. 1913, lxviii, 292.
[4] *Arch. Int. Med.*, 1913, xii, 236; *Jour. Amer. Med. Assn.*, 1913, lxi, 1803.
[5] *Jour. Amer. Med. Assn.*, 1913, lxi, 2122.

PLATE XVI

Hodgkin's Disease.

Cervical, mediastinal, axillary, bronchial, and retroperitoneal lymph nodes.

involvement is widespread, great collections of tumors are seen in the neck, thorax, axillæ, retroperitoneum, mesentery, and inguinal regions. But wherever the tumors are found, whether they are generalized or confined to one situation, such as the neck or mediastinum, their general appearance is much the same. When the lobulated tumor masses are examined carefully one sees that they are composed of separate nodules, varying greatly in size, the larger nodules usually forming the central portion of the masses, while smaller tumors are attached to the superficial regions. In typical instances the nodes are oval or round, often somewhat irregular, but still presenting a smooth surface; they are not fused, but are discrete and separate, even in the largest masses, for the single tumors are only held together by loose connective tissue. Often by rapid dissection these large, conglomerate tumors may be resolved into single, smooth nodes. The color is white, pinkish, semitranslucent gray, or a delicate cream tint.

The nodes vary a great deal in consistency, and, indeed, it has been common since Virchow's description of the condition to distinguish between the hard and soft forms. This distinction is, however, more or less artificial, for the hardness or softness of the nodes depends upon the progressive changes which have taken place in the tumors themselves. In certain cases all the glands may be soft, some giving a distinctly elastic sensation on palpation, others almost suggesting the presence of fluid, so near is the feeling to one of fluctuation; while, again, all the tumors may be firm or extremely hard. Occasionally, in a single group of tumors some are soft, some elastic, some firm, and others again seem almost to fluctuate. Usually the smallest or youngest nodes are soft, while the larger ones are firm; but the reverse may be true, and the size of the tumor may be no index to its consistency (Plate XVI).

The cut section is often very characteristic. The surface of the softer glands is pinkish gray, semitranslucent, rather juicy, and either bulging or slightly lobulated. The latter appearance is more pronounced in the larger tumors. The irregular character is produced by depressed bands of yellowish tissue which sometimes extend from the capsule toward the centre of the mass, sometimes cut up the surface irregularly, but in any event leave bulging areas of semitranslucent gray tissue between them. In the firmer nodes the yellowish bands are thick, numerous, and predominate, while the very hardest nodes may be entirely composed of this yellowish or white, somewhat opaque tissue. Rarely small, opaque gray or yellow foci of softening are scattered over the cut surface.

Although in the majority of instances the tumors present the appearance just described, their character may be altered by certain influences. The discrete nature of the single tumors has always been emphasized in the descriptions, but as Yamaski and Diedrich have described, the growths at times appear to extend through the capsule into surrounding tissues in much the same way as a new growth. It must be noted, nevertheless, that the tumors extend in bulk, having a regular margin along the line of advancement compressing the surrounding tissue, and thus forming a false capsule. They rarely infiltrate in an irregular manner. In the series of autopsies at the Pennsylvania Hospital, Philadelphia, a

very rapidly fatal case which exemplifies this type of growth was studied. The lower portion of the neck and supraclavicular regions were filled with tumors which extended into the muscles and involved the thyroid gland. Into the neighboring muscles, the granulomatous mass extended irregularly, giving the impression almost of an infiltrating tumor. Occasionally solitary nodules appear in or between the muscles. This is most frequently seen in the pectoral region. Rarely the granulomatous tissue involves the periosteum.

If the nodes become secondarily infected, they may be found matted together, firmly adherent, and surrounded by inflammatory tissue. The same condition is often noted after prolonged treatment by the *x*-rays. In old tumors bright yellow areas of fatty degeneration may be seen, or at times small grayish or yellowish areas of necrosis are scattered over the cut surface. In rare instances cone-shaped hemorrhagic areas may be seen at the periphery of the gland, the base of the cone lying beneath the capusle. The centre of the area is necrotic, the periphery composed of a hemorrhagic area.

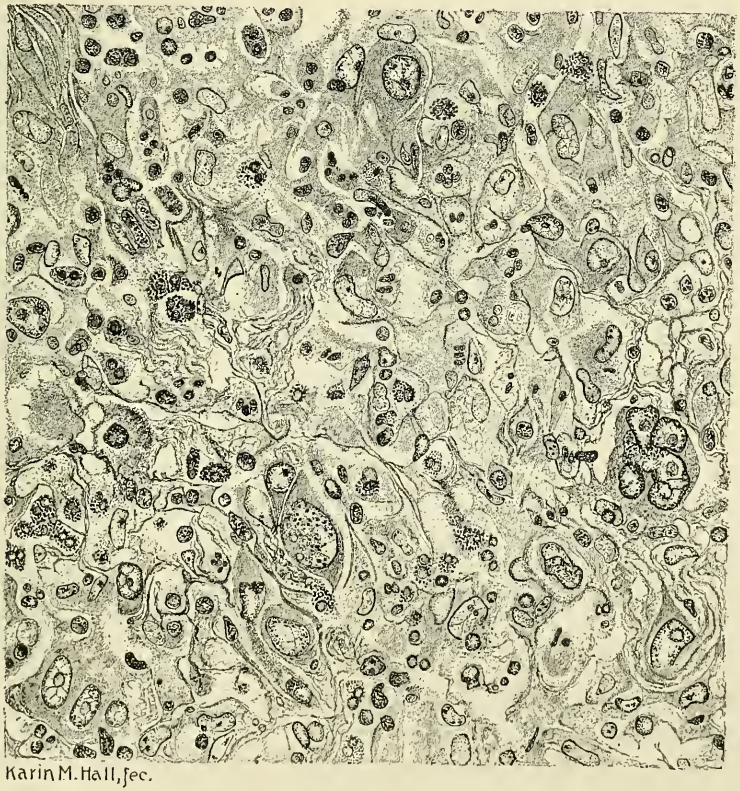
The histology of the lymphomatous nodules, formerly so imperfectly understood, has now received very careful study, and the conclusion reached by most investigators is that the disease presents a characteristic and readily recognizable, though somewhat complex picture.

The first well-marked microscopic changes are seen in the smallest glands or often in the nodes immediately adjacent to the main tumor masses. They consist in a hyperplasia of the lymphoid cells with active proliferation at the germinal centres of the lymphoid follicles. There is besides increased vascularity and beginning proliferation of the reticular endothelium. Benda likens the changes to an early inflammatory process. The normal structure of the node is fairly well preserved. The lymph sinuses are dilated, and contain small and large lymphocytes and polymorphonuclear leukocytes, along with which eosinophiles and endothelial cells are frequently seen. In the endothelial cells covering the reticulum of the node karyokinetic figures may usually be found, and are often numerous. The reticulum itself is prominent. Although the lymphoid cell predominates in the follicles and lymph cords, still one may see many other types of cells mixed in with them and in greater numbers than occurs normally. Large lymphocytes, epithelioid cells, plasma cells, mast cells, and eosinophilic leukocytes are often distributed quite plentifully.

As the process grows slightly older, the proliferation of cells increases and the thickening of the reticulum becomes more noticeable, until at quite an early date almost all traces of the normal structures are lost. Only here and there can be seen indefinite remains of the lymphoid follicles, centred, perhaps, by a germinal centre; or a few spaces representing what is left of the lymph sinuses. At this period sections have quite a uniform appearance. The node is surrounded by a definite capsule often somewhat thickened but distinct. Throughout the node there is a reticulum forming a meshwork of varying coarseness, which encloses cells of different types; while narrow bands of young connective tissue usually divide the glands into irregular lobules. Lying in the meshes

of the network one sees small and large lymphocytes, plasma cells, polymorphonuclear leukocytes, eosinophiles, epithelioid cells, and uninuclear and multinuclear giant cells. These various elements are not arranged to form any definite structures, but simply fill in the spaces of the reticulum to make one solid whole. The various cell types are not, however, equally distributed through the glands. Whereas, in some portions lymphoid cells predominate, suggesting the remains of ancient follicles, in other parts epithelioid cells, giant cells, or even eosinophiles, may be the prevailing elements. The tumor at this stage represents the soft type of lymphoma (Fig. 58).

FIG. 58



Hodgkin's disease. Lymph node, high power drawing.

In intermediate periods the multinucleated giant cells are often one of the most constant and striking features. As suggested by Reed and others they are probably derived from the uninuclear giant cells, which in turn take their origin from the reticular endothelium. The uninuclear giant cell is very irregular in form and has a clear protoplasm containing one or several pale nuclei, which often take on the most bizarre shapes. Outlining the nucleus is a fine, deeply staining vein of chromatin, and

in the centre a well-defined network with one or several deeply staining and sharply defined nucleoli. The multinucleated cell is a further development of the uninuclear variety where the nucleus has undergone either direct or indirect division. In the larger multinucleated giant cells, which are sometimes of astonishing size, the nuclei, often four to ten in number, are heaped together in the periphery, or centre of the cell, and their general pallor, contrasting with the deeply colored definite chromatin network and prominent nucleoli, with their very irregular forms, gives the cells a most characteristic appearance. A second form of giant cell is sometimes seen. This one differs from the first in that the nuclei stain deeply and are arranged in the shape of a horseshoe about the periphery of the cells. These cells resemble very closely the Langhans giant cells of tuberculosis.

Occasionally the proliferation of the endothelioid cells is so extensive that they form large masses and solid columns, filling the lymph sinuses, and since the cell outline is indistinct, these cords of cells may give the appearance of masses of protoplasm containing many nuclei.

Together with the extensive cellular proliferation, cellular degeneration is also to be noted. Nuclear fragments are scattered through portions of the glands, and not infrequently areas of necrosis are found. These may be sufficiently large to be seen macroscopically, when they appear as small, yellow areas. They are infiltrated with fibrin and usually surrounded by moderate numbers of leukocytes. Frequently these leukocytes have eosinophilic granules, and though it is not always the case, yet in many instances the eosinophiles, which are often scattered in profusion through the glands are gathered about the necrotic foci in vast numbers. The cells may also undergo fatty degeneration.

As the disease progresses the connective tissue increases. Coarse, fibrous bands run from the capsule into the tumor, cutting it into lobules, and the reticulum thickens and becomes more prominent, thus narrowing the cellular spaces of the mesh (Fig. 59 and Plate XVII). Occasionally it undergoes hyaline degeneration, then the gland looks as if formed of a very coarse hyaline mesh work enclosing a few cells in the interstices. In still later stages the tumors are composed principally of fibrous tissue varying in cellular contents. The cellular part of the tumor is restricted to small islands lying between the coarse, connective-tissue bands. Sometimes there may be many giant cells, often very large in size. Finally, these cellular islands are replaced entirely or in part by connective tissue, and only here and there small collections are left to remind one of the former structure so rich in different varieties of cells.

While in the early stages the structures are very cellular, in the later stages the nodes are almost completely converted into fibrous tissue, and without studying the development of the process the first and last stages might almost be mistaken for different conditions. This sequence of events does not march regularly through all the groups of enlarged nodes. Some, even large ones, may be quite cellular and soft, while other smaller tumors are hard and show much new connective-tissue formation. Neither do single nodes always show the same stage of

PLATE XVII

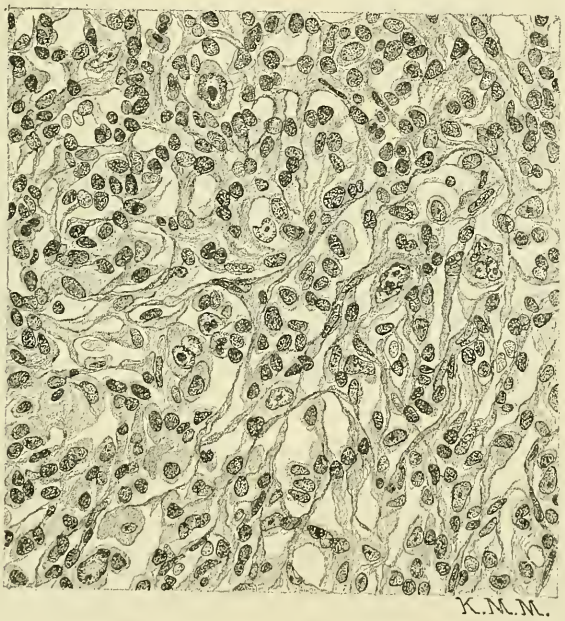
Lymph Node, showing Increase of Reticulum.

Mallory's connective-tissue stain.

development throughout, for parts may be quite cellular, while the remainder is composed principally of fibrous tissue.

Aside from the progressive increase in the size of the nodes, there is usually an increase in numbers. As the preëxisting nodes are rendered functionless in Hodgkin's disease, it is probable that an attempt is made on the part of the tissues to produce new glands. This regenerative process starts in small masses of lymphoid cells which are to be regarded as the anlage of the lymph glands and are to be found in the connective tissue surrounding the tumor masses. As they develop, these embryonic organs become involved in the general lymphatic disturbance, and instead of pursuing their normal growth are transformed into lymphomatous nodules and continue as such.

FIG. 59



Hodgkin's disease. Lymph node, showing increase of reticulum.

The general character of the growth, the thickened reticular mesh enclosing lymphoid cells, epithelioid cells, plasma cells, giant cells, and eosinophilic leukocytes, form a picture so characteristic that it cannot be mistaken for any other condition. Among the cell types the eosinophiles have been emphasized as particularly characteristic. These cells may be either polymorphonuclear, showing two or more lobes, or uninuclear. The former variety is more common, but the latter may also occur in comparatively large numbers. The eosinophiles are frequently abundant and are rarely absent in any case. Reed,[1] in particular, finding them in large proportion of her cases, lays special stress upon their

[1] *Johns Hopkins Hosp. Rep.*, 1902, x, 133.

presence as assisting in the diagnosis of the affection. Although small numbers of eosinophilic leukocytes are seen in lymph nodes which were the seat of tuberculosis, sarcoma, and metastatic carcinoma, they rarely attract particular attention. A profusion of eosinophilic leukocytes has been observed in the lymph nodes from fatal cases of diphtheria and scarlet fever, but except for a few such conditions, Hodgkin's disease seems to be one of the only pathological conditions affecting lymph nodes in which the acidophilic cells play such an important rôle. The exact relation of these cells to the pathological process and their significance has not as yet been determined.

Secondary Growths.—The lymph nodes must be considered as the most important seat of the disease, but the other organs are not exempt, for secondary deposits may occur in many different situations. It was first thought that these secondary growths were of a true metastatic nature, but it is now usually believed that they are not true metastases, but growths arising from the lymphoid tissues of the organ in which they are situated.

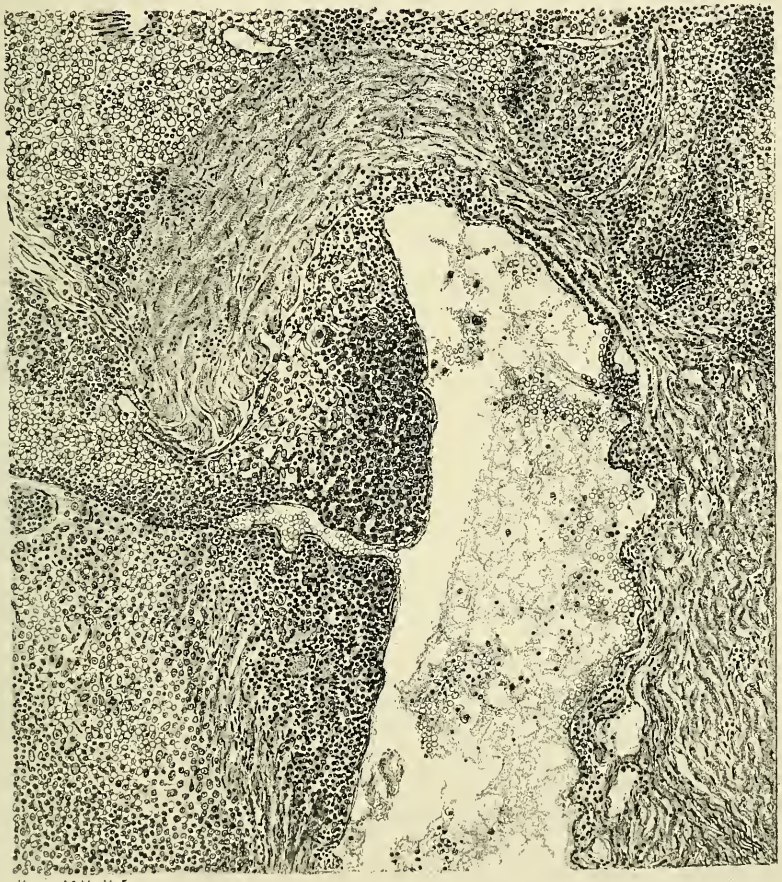
Fig. 60

Hodgkin's disease. Spleen.

Spleen.—If the spleen is the seat of secondary growths, it is often enlarged, but rarely to a very great size, although in unusual cases, as one in the writer's series, the organ weighed 1850 grams. Cases have been reported, however, in which both during life and at autopsy, the enlargement of the spleen was the most prominent feature, and a few doubtful cases are on record, such as those of Symmers and Wade, in which the spleen was supposed to be the primary and solitary site of the disease. It is usually regular, preserving the normal contour, and is firm. The capsule may be covered with fibrous adhesions. Sometimes the surface is slightly nodular owing to the protrusion of the lymphomatous nodules beneath the capsule. The organ usually presents a mottled or marbled appearance, which is much more marked on section, and is red, purple, and grayish-white. When the secondary deposits are numerous, the red pulp is streaked and mottled with irregular pearly-white or yellowish lines and masses varying in size, according to the extent of the process. The cut surface is compared by many to red porphyry. On close inspection it will be seen that the smaller and younger growths follow rather closely the lines of the trabeculæ, and the smallest masses are rarely to be distinguished from the Malpighian bodies, which

are usually enlarged. If the process is but slightly advanced, only a few small, scattered, semitranslucent, grayish areas may be seen, and the spleen may be very slightly, if at all, enlarged. Besides the typical tumor growths, there may also be infarctions along the margins of the organ (Fig. 60).

Fig. 61



Hodgkin's disease. Growth of lymphomatous nodule into vein of the spleen.

Microscopically, the gray or whitish nodules appear in structure exactly like the lymph nodes. The youngest growths are always found in the Malpighian bodies. As they become older and larger this relationship can no longer be traced. There may be much new connective-tissue formation and many foci of necrosis. The margins are usually well defined and the pulp spaces about the advancing edge are often flattened out, forming an apparent capsule. The growths, pushing their way, may extend into the bloodvessels (Fig. 61).

Liver.—This may be enlarged, but it is not nearly so often increased in size as the spleen. Besides the secondary deposits, which are occasionally

seen and are scattered over the surface in the portal areas as pearly-white masses of various size, there may be fatty degeneration or a slight perilobular cirrhosis. The secondary deposits usually arise in the lymphoid tissue of the portal spaces and pursue much the same course as the growths in the spleen.

Other Organs.—More rarely lymphomatous nodules are found in the kidney, which, except for this lesion, shows no other characteristic changes. Occasionally the lungs are extensively involved with secondary growths. Here, as in the other organs, the growths have the same general appearance and microscopic structure as is seen in the lymph nodes. The youngest nodules are found about the bronchi, and start their growth in the masses of lymphoid cells scattered through the lungs in these situations. Indeed, as Fischer has stated, practically any organ or even tissue of the body, if it contains lymphoid tissue normally, may be the seat of secondary lymphomas. Growths have been described in the pericardium, pleura, thymus, tonsils, muscles, bone marrow, periosteum, skin (Crosz), and gastro-intestinal tract.

In the bone marrow true growths occur not infrequently, but undoubtedly, many of the cases formerly called myelogenous pseudoleukemia are, in fact, instances of multiple myeloma. Besides the secondary growths, such alterations in the blood-forming cells as an increase of lymphocytes and increase of eosinophilic myelocytes has been noted.

A condition which by some has been thought to have a possible connection with Hodgkin's disease is the growth of lymphomatous tumors which occurs in the parotid and lacrimal glands. First described by von Mikulicz, the disease has been studied subsequently by several investigators. The histological picture, according to Minelli,[1] is not unlike that described for Hodgkin's disease, although it may be altogether a different process.

Symptoms.—Onset.—The first point to attract attention in the great majority of cases is swelling of the superficial lymph glands; and not only is it the first manifestation, but often, in the early part of the affection, the only one which disturbs the patient. For during what may be called the first stage of the disease there is no anemia, no loss of weight, and no general ill health, so that the patient may come in good physical condition to ask advice about the tumor masses which inconvenience him or are disfiguring. If, however, the deep glands instead of the superficial glands are primarily involved, the onset is more insidious. Occasionally there is a history of malaise or attacks of fever. Rarely the disease progresses silently until what may be termed the second stage is reached, when symptoms referable to pressure exerted by the deep glands upon the surrounding structures make their appearance. Dyspnœa, jaundice, pain in the arms, sciatica, œdema of the legs and abdomen, or violent abdominal pain may be the first manifestations of the disease. Occasionally the onset is very insidious with fever, malaise, and enlargement only of the deep glands. In such instances the superficial glands may not be enlarged.

[1] *Virchows Archiv*, 1906, clxxxv, 117.

Swelling of the superficial lymph glands occurred as the first symptom in 52 out of 78 of Gowers' collected cases, and in 71 of the 86 cases tabulated by the writer. The favorite situation for the glands to make their appearance is in the cervical region. Thus, in Gowers' 78 cases primary enlargement of the glands of the neck was noted 36 times, and in the present series 57 times. The order of frequency in which the other groups are affected first is as follows: (1) Axillary, (2) inguinal, (3) bronchial, (4) mediastinal, and (5) retroperitoneal. As accurately as can be told from the histories, the axillary glands were the first to enlarge in 4 cases of this series, the retroperitoneal in 4, the mediastinal in 2, the inguinal and the epitrochlear in one each.

Glandular Swelling.—In the cervical region the disease seems to have a predilection for the nodes situated in the posterior triangle, and although the submental and submaxillary groups may be involved either early or late, it is more usual to find the tumors above the clavicles or in the postauricular region. Usually the disease starts in one side of the neck, and there seems to be no preference for either side, since the right and the left are affected about equally. The swelling may be entirely confined to the right or the left side, or may spread rapidly or only after a period of months or years to the opposite side. The glands may swell on both sides at the same time.

Having once made its appearance, the rapidity with which the disease progresses is somewhat variable. In cases running an acute course, one group of glands after another becomes enlarged until all the superficial and deep glands are swollen to an enormous size. The progress usually takes place in an orderly manner, the disease spreading from one group of nodes to its neighbor, so that there may be a descent down the cervical chain to the supraclavicular, the axillary and mediastinal; or an ascent from the inguinal nodes along the pelvic chain of lymphatics to the retroperitoneal glands. In the more chronic cases the disease, although progressive, is slow in its march, and stops for months or longer with the enlargement of a single group of glands. But sometimes, after months of quiescence, the disease fairly bursts into activity and spreads with great rapidity. Finally, there is a group of cases in which the swelling is confined throughout the disease to two or three groups of lymph nodes, or even to a single group. In such instances the development of the tumors is usually slow, and unless accidents happen the affection may be prolonged over several years. At any time, however, a general eruption of tumor masses may take place. It is said that, of themselves, single glands may vary in size from time to time.

The superficial swellings are painless, and unless they become the seat of a secondary infection they are not tender to touch. The tumors can readily be mapped out beneath the skin, and when they have not attained a great size can be freely moved about and felt as discrete, oval, round, or slightly irregular masses of various sizes. Often they are moderately soft and elastic, sometimes almost giving the sensation of fluctuation; but in other cases they are quite firm or even of an extreme hardness. When the tumors are very large it is more difficult to move them about, for they are packed closely together and the skin is stretched tightly

over them. But even in the largest tumors, which may feel like solid lobulated masses, one can find glands about the margins, which are regular and freely movable. The tumors are never adherent or matted together except from some secondary cause. After prolonged *x*-ray treatment the nodes may be densely matted together and adherent to the surrounding tissues. They do not soften, break down, or ulcerate through the skin. Over the very large masses the skin may be stretched and taut, so that it is smooth and shiny, but it is not reddened or inflamed.

As the disease advances and the tumor masses grow in size, a series of *pressure* symptoms usually develops, which are varied in their nature and depend naturally upon the situation of the enlarged glands. This may be considered as the second stage of the disease. With the enlargement of the cervical nodes the trachea may be compressed, giving rise to cough and varying degrees of dyspnœa. The latter symptom is unfortunately only too common, and of all, perhaps the most horrible. Sitting up in bed, with great deforming tumor masses bulging from the sides of his neck, and limiting the motion of his head, the patient, drooling saliva, his mouth open like a fish, gasps for breath. Very slowly, but very surely, the dyspnœa increases, until he dies, strangling. (Plates XVIII and XIX.)

Occasionally the larynx and trachea are pushed far to one side. There may be paralysis of one or both recurrent laryngeal nerves. Pressure upon the vessels of the neck gives rise to cyanosis and œdema of the face. One of the jugular veins may become thrombosed. In certain instances there is a fair degree of exophthalmos. Paralysis and marked swelling of the left side of the tongue occurred in one instance. Besides this there was difficulty in deglutition, pain on the left side of the face, and paralysis of the sixth nerve on the left side. If the tumors involve the tonsils and posterior pharynx, which occasionally happens, the patients are forced to breathe through the mouth, which they hold open. Deafness may develop. Dysphagia is not at all uncommon.

Masses in the mediastinum may cause dyspnœa, cough, and dysphagia, or if they press upon the pericardium they may impede the heart's action. Pressure upon the great vessels causes dilatation of the veins or œdema of the upper extremities; while pressure from enlarged axillary glands upon the vessels and nerves may give rise to swelling of the hands and arms, or pain in the arms. With enlargement of the bronchial and mediastinal glands, effusion into the pleural sacs occurs in a certain number of instances. This is usually seen only late in the disease. The fluid is most often serous, although chylous effusions are mentioned. Edsall[1] has described in one case a curious type of milky, albuminous effusion into the pleura which at first sight appeared to be chylous in character. A very marked emphysema may develop.

In the abdomen, groups of enlarged nodes may bring about various complications. Jaundice not infrequently develops as a result of the pressure by gastrohepatic glands upon the bile ducts; and mild symp-

[1] *New York Med. Jour.*, 1905, lxxxii, 838, 901.

PLATE XVIII

Hodgkin's Disease

PLATE XIX

Hodgkin's Disease.

toms of pyloric obstruction may accompany the swelling of glands about the pylorus. Pain, simulating that in appendicitis, may accompany swelling of the mesenteric nodes. Following pressure by enlarged retroperitoneal, iliac, and inguinal masses, violent and persistent pains in the legs or œdema of the lower extremities may develop. Ascites is not uncommon, and there may be anasarca. In rare instances the vertebræ become involved and symptoms may arise from pressure upon the cord. In one of my cases there was spastic paraplegia.

Secondary Growth.—Besides the disturbances caused by enlargement of the glands themselves, symptoms may arise from the growth of secondary masses. When tumor masses make their appearance in the lung, there may be cough and some expectoration. Unless they are very massive the pulmonary growths cannot always be detected, although areas of dulness, combined with harsh breathing and rales, may raise suspicion of their presence. The *x*-rays should assist greatly in determining whether or not the lungs are involved. Definite circulatory disturbances are rare. Violent gastro-intestinal symptoms may result from the development of a growth in the lymphoid tissues of the wall of the stomach or intestines.

In the majority of cases the *spleen* is palpable and often greatly enlarged, although it seldom reaches the size which it attains in leukemia. An involvement of the spleen was present in 34 of 58 cases in which the condition of this organ was noted. The enlargement depends principally upon the number and size of the secondary growths in that organ. It is exceedingly rare for the nodules to be sufficiently prominent to be felt through the abdominal wall. In a few instances the spleen is the only organ that shows noticeable enlargement during life. In one of my cases there was progressive enlargement of the spleen associated with deepening jaundice and without swelling of the superficial lymph nodes. At autopsy, not only the spleen but the retroperitoneal nodes were involved and pressed upon the bile duct. The *liver* is increased in size in a smaller proportion of cases. It was the seat of secondary deposits in 26 of 52 cases. The enlargement may be due to the secondary deposits, but perhaps is more commonly caused by a fatty degeneration which occurs not infrequently in this disease. The kidneys attract little or no attention. There is nothing characteristic in the urinary secretion, and if secondary growths do occur in this organ their presence may be and usually is only determined at autopsy. Secondary granulomata may appear with some frequency in the pectoral region, forming large masses beneath the clavicle or about the breasts. Often they are in the muscles of this region but they may actually involve the breast tissue. In some instances the nodules lie directly beneath or, indeed, actually in the skin. In the rare instances in which the periosteum is involved there is pain over the affected bones.

Much interest is attached to the *cutaneous* changes which may arise, Aside from the pigmentation which may follow the use of arsenic, a brownish discoloration or mottling which is usually associated with enlargement of the retroperitoneal lymph nodes is seen occasionally. The origin of this pigmentation has been ascribed by some observers

to pressure upon the cœliac plexus by tumor masses. Pruritus is an exceedingly annoying symptom, which may be met with in some cases. It may be persistent and severe. This symptom was noted in three of the writer's collected cases. Gowers mentions the occurrence of hemorrhages in the skin and mucous membranes. This is certainly not as common as the hemorrhages which occur in leukemia. It is not mentioned once in the 86 collected cases.

Fever.—This is a fairly constant feature, although at times it may be absent and the disease runs an afebrile course. It is customary to divide the febrile cases into three groups. In one class of cases there is a continued mild fever, slightly irregular, varying a few degrees and rarely going above 101° or 102°. This slight rise of temperature may persist for months or even longer, and in certain cases lasts throughout the course. But more often during the later stages the character of the temperature curve changes to one of the two other types. In the second group of cases the temperature is quite irregular, high, and intermittent, showing perhaps diurnal remissions of several degrees. With the elevation of temperature there may be chilly sensations or actual chills and sweats, even when there is no secondary infection. In the third group the type of the fever is exceedingly interesting. It is relapsing, and periods of pyrexia of several days' or even weeks' duration alternate with longer or shorter periods of apyrexia. This condition may continue for many months. Murchison[1] drew attention to these relapsing fevers in Hodgkin's disease, and later Ebstein[2] and Pel[3] described cases illustrating a condition in children to which Ebstein at first gave the name of "chronic relapsing fever." Pel and, later, Ebstein too decided that these cases were examples of Hodgkin's disease showing a curious type of relapsing fever. Since that time the relapsing type of fever has been frequently observed. It is possible that in such cases the rise of temperature is due to a secondary infection of some sort. Fischer, in one instance, isolated staphylococci in cultures from the blood during the attacks of fever which lasted ten to twelve days, while cultures during the afebrile attacks gave no growth of bacteria. Ruffin,[4] on the other hand, has reported a case in which there were four periods of pyrexia, each of which lasted from ten to thirty-five days, and in which blood cultures during the fever periods always gave negative results.

Blood Changes.—The anemia, which generally develops as the disease progresses, is one of the characteristic symptoms. It is ordinarily of a secondary type. In long-continuted and chronic cases the loss of hemoglobin and decrease of red blood corpuscles takes place slowly; but when the disease runs a rapid course the anemia soon becomes marked, and before death it may be very severe. Not uncommonly the hemoglobin falls to 30 or 40 per cent., and the red blood corpuscles to 3,000,000 or 2,000,000 per cmm. Occasionally the anemia is of an extreme grade. In one of the cases which occurred at the Pennsylvania Hospital, Philadelphia, the hemoglobin, some days before death, registered 22 per cent.,

[1] *Transactions of the Pathological Society*, 1870, xxi, 372.
[2] *Berl. klin. Woch.*, 1887, xxiv, 565, 837.
[3] *Ibid.*, 644.
[4] *Am. Jour. Med. Sci.*, 1906, cxxxi, 587.

and the red blood corpuscles numbered 980,000. Nucleated red blood corpuscles are rarely found.

The white blood corpuscles show no characteristic or constant alterations. Their number may vary considerably, but, as a rule, these elements, in proportion to the number of red blood corpuscles, are increased rather than decreased. Most frequently the leukocytes average between 10,000 and 20,000. Of 38 of the collected cases in which a blood count is recorded, the leukocytes in 11 instances were below 10,000, in 21 instances between 10,000 and 20,000, and in 6 instances above 20,000. Pinkus[1] holds that an increase in the small, mononuclear cells is characteristic of the disease, and, indeed, lays a great deal of stress on this point. A review of the recent literature, however, does not seem to uphold his contention. Of 31 of the collected cases in which differential counts were recorded, the polymorphonuclear leukocytes in 21 formed over 70 per cent. of the cells at every count; in 4 cases they were above 70 per cent. in one count, and in 1 case above 70 per cent. in two counts. In only 5 cases did the polymorphonuclear leukocytes persistently form less than 70 per cent. of the white cells. The lymphocytes in 15 cases formed less than 20 per cent. of the total number of white cells, while in only 6 instances were they at any time above 30 per cent. A marked leukocytosis and a relative increase of the lymphocytes never occurred together. Steiger,[2] who has recently studied this question, finds a lymphocytosis during the early stages of the disease, which gives place to a polymorphonuclear leukocytosis during the acute stages. The relative eosinophilia is most marked when there are necroses in the glands. In a few cases of Hodgkin's disease there is a relative and absolute increase in the eosinophilic leukocytes. In 3 of the cases in this series Pepper found a relative eosinophilia of from 8 to 13 per cent. Lincoln[3] has called attention to this point and discusses the question at some length. The latter author reports a case in which the eosinophiles formed from 43.4 to 70 per cent. of the total number of white cells. Bunting has called attention to the constant increase in the platelets of the blood, and considers this quite characteristic.

The *course* and *progress* of the disease vary considerably according to the location of the enlarged glands, the rapidity of their growth, and the involvement of other structures. It has been common to recognize an *acute* form of the disease in which the entire duration of life after the appearance of symptoms is but a few weeks. In such cases the enlargement of the lymph nodes occurs very rapidly, and extends swiftly. There is usually high fever which is constant or remittent, and a severe and progressing anemia. The case from which the glands pictured in Plate XVI were removed lived only three months. Ziegler and Peise have reported instances in which the duration was but a few weeks.

The *localized* form is perhaps the best recognized and the commonest. In this group the disease runs rather a chronic course, and remains for comparatively long periods confined to one region of the body. The

[1] *Nothnagel's System*, American edition, "Diseases of the Blood."
[2] *Berl. klin. Woch.*, 1913, 1, 2129.
[3] *Boston Med. and Surg. Jour.*, Fitz's *Festschrift*, 1908, clviii, 677.

cervical glands are the most commonly affected, and the solitary masses grow slowly and painlessly often only on one side for months or even two or three years. The constitutional disturbances are slight. There frequently is no fever, though occasionally such cases may present the relapsing type of fever. The anemia is of mild degree. At any time, however, during this comparatively benign course, and sometimes following surgical intervention, the process may burst forth into great activity and spread rapidly, ending in what one may call the generalized form.

In the *generalized* type there is the most widespread glandular enlargement. In a few cases, without prodromes, the disease may start as this form. Cervical, submental, axillary, epitrochlear, inguinal, the abdominal, the thoracic, and even the popliteal glands become enlarged and rapidly grow in size. Masses may appear in such unusual situations as the infraclavicular and pectoral regions. The spleen and liver become palpable. Fever soon forms a prominent part of the picture and is irregular, remittent, or definitely recurrent. The patient becomes anemic, emaciated, or may develop œdema of the extremities. There is often a leukocytosis. Pigmentation of the skin in brownish patches, or as a diffuse discoloration, and pruritus, are oftenest seen in this type. The outlook is hopeless and the patient dies of some secondary infection or of exhaustion.

The most distressing form is that which develops as a *mediastinal* tumor. In some of these cases it is possible that the granuloma arises in the thymus. Though such cases may form a part of the generalized type still there are instances of Hodgkin's disease in which the masses are confined almost exclusively to the mediastinal and lower cervical regions. The predominant symptoms are those of pressure; dyspnœa, dysphagia, cyanosis, dilatation of the superficial veins of the neck and thorax are prominent features. Pressure may be exerted upon the recurrent laryngeal nerves, the sympathetic or the brachial plexus. The trachea is distorted and often compressed to such an extent that the enlarging granulomatous mass finally strangles the patient.

More uncommon but less distressing is the *splenomegalous* form in which the disease affects particularly the spleen. There may be slight or absolutely no superficial glandular enlargement, but often the swelling of the mesenteric and retroperitoneal nodes give rise to abdominal signs and symptoms. Together with the enlarged spleen there may be abdominal pain, gastric or intestinal disturbances, jaundice, œdema of one or both legs or pain in the lower extremities. The anemia, cachexia, and fever are sometimes pronounced.

And, finally, a so-called *larval* or typhoid form has been described, especially by Ziegler and Rosenthal,[1] in which the glandular enlargement is entirely confined to the retroperitoneal and retromediastinal groups. The onset is insidous and manifests itself by gradual loss of strength and weight, vague abdominal pains, sometimes night sweats, headache, lassitude, and occasional fever. As the disease advances, the fever

[1] *Berl. klin. Woch.*, 1913, 1, 2382.

becomes constant or shows remissions not unlike relapses in typhoid fever. There may be vomiting and diarrhœa, a positive diazo-reaction in the urine, and, unlike most cases, marked leukopenia with severe secondary anemia. Cases are on record in which the leukocytes in the terminal stage have fallen to as low a figure as 2000 or 1000 per cmm. The spleen and sometimes the liver are enlarged. Mild jaundice has been noticed in some cases. It the later stages the picture may simulate typhoid fever very closely.

Diagnosis.—Owing in part to the great confusion in nomenclature, but principally to a lack of exact knowledge concerning the nature of the process, a number of conditions have been grouped under the heading of pseudoleukemia, which are now considered to be different and distinct diseases. There are a number of the diseases of the lymph nodes and spleen which must be definitely distinguished both on clinical and pathological grounds from Hodgkin's disease.

Splenic anemia and the various forms of *splenomegaly,* once thought by many to be a splenic form of pseudoleukemia, are now known to be absolutely unlike Hodgkin's disease. The work of many writers goes to show that the pathological changes in splenic anemia are either of a chronic inflammatory nature with connective-tissue overgrowth or, in the Gaucher type, consist in the extensive proliferation of tumor-like nodules. Rarely is there any difficulty in distinguishing splenic anemia from Hodgkin's disease during life. Only in those cases of Hodgkin's disease in which the spleen is greatly increased in size and the enlargement of the lymph nodes is confined to the abdominal groups can any question arise as to the diagnosis between the two conditions. Even so, it may be possible to feel masses in the abdomen on deep palpation; or there may be pressure symptoms such as jaundice, œdema of the lower extremities, or pain in the legs, which lead one to suspect the presence of hidden tumor masses. Any swelling of the superficial lymph nodes rules out splenic anemia, for in this disease the glands are not enlarged. The unusual cases of Hodgkin's disease without superficial glandular enlargement have been mistaken for various diseases and so far have not been recognized during life.

The general glandular enlargement seen in *syphilis* is not liable to be mistaken for Hodgkin's disease. Tumors of the mediastinum and neck may lead to confusion. In a patient at the Philadelphia Hospital an enormous multilobulated tumor of the thyroid gland was mistaken for a group of enlarged lymph glands, and considered to be Hodgkin's disease until the mistake was discovered at autopsy.

The conditions which may most readily be mistaken for Hodgkin's disease are lymphosarcoma, lymphatic leukemia, tuberculosis, and acute inflammatory enlargements of the lymph nodes.

In considering the complex question of malignant new growths of the lymph nodes and their differentiation from Hodgkin's disease, it is necessary to bear in mind certain distinctions which have been made, by such authors as Paltauf and Sternberg, between the various types of sarcoma of the lymph glands, round-cell sarcoma, mixed-cell sarcoma, spindle-cell sarcoma, and the tumors probably arising from

the endothelial cells of the lymph glands, from the types of tumor classified by Kundrat[1] as lymphosarcoma, a tumor arising from the lymphoid tissue of the lymph nodes.

The various types of *sarcoma* of the lymph nodes, tumors of rare occurrence, are in general not very difficult to differentiate from Hodgkin's disease. Their growth is rapid, they usually give pain, the tumors infiltrate the surrounding tissue, they may involve the skin, break down and ulcerate, and often form metastases. At times, however, the tumors grow more slowly, forming large, irregular masses in the neck or axilla. The disease may not be accompanied by pain, and the picture resembles very closely Hodgkin's disease. The true nature of the growth may not be determined until a nodule is removed for diagnosis.

The second group of lymph node tumors, *lymphosarcoma*, was originally divided into two varieties: one a localized growth of a single group of lymph nodes, the other a generalized enlargement of lymphatic structures, with infiltrating tumors in various organs. In cases belonging to the second group, it is very frequent to find involvement of the walls of the alimentary canal and serous surfaces. In a large proportion of cases the tumor invades the wall of the stomach or intestines or grows upon the surface of the pleura. Since many of these growths occur within the abdomen or thorax, 3 of MacCallum's[2] 8 cases being essentially intrathoracic, although in 2 there were cervical tumors, and 5 being intraabdominal, it is not usual to confuse them during life with Hodgkin's disease. When, however, the growths are seen in superficial regions, it is unquestionably very difficult to make an accurate diagnosis, and these cases may be mistaken for Hodgkin's disease. At times the evidence of involvement of the pleural or other serous surfaces, which is rare in Hodgkin's disease, and the infiltrating and immovable character of the superficial tumors, will serve as points of differentiation. When, however, the lymphosarcomatous tumors are localized in the axilla, groin or cervical region, and are, as sometimes happens, quite separate, movable, regular and free from tenderness, it is absolutely impossible, without microscopic examination of a gland to differentiate the true condition.

Recently several classifications of the so-called *lymphomatoses* have been proposed in an endeavor to group these affections together under one heading. It must be remembered that in these classifications the term pseudoleukemia refers not to the disease under discussion, Hodgkin's disease, but to an entirely different affection. Sternberg[3] recognized a condition which he called pseudoleukemia, distinguished from lymphatic leukemia only by the absence of leukemic changes in the blood. There is a general glandular enlargement, and the lymph glands show the same histological picture as in lymphatic leukemia. Pseudoleukemia, as the term occurs in the other classifications, has much the same significance. Türck,[4] for instance, for some time, has brought under the heading of

[1] *Wien. klin. Woch.*, 1893, vi, 211, 234.
[2] *Johns Hopkins Hospital Bulletin*, 1907, xviii, 337.
[3] *Erg. der allg. und path. Anat.*, Lubarsch-Ostertag, 1905, ninth year, p. 441.
[4] *Wien. klin. Woch.*, 1899, No. 40, p. 985; *Berl. klin. Woch.*, 1901, No. 38, p. 965; *Wien. klin. Woch.*, 1903, No. 39, p. 1073.

the lymphatoses the acute and chronic varieties of lymphatic leukemia, pseudoleukemia, chlorosis, and lymphosarcoma, suggesting that the difference between them is rather one of degree than kind; while Pappenheim[1] believes there is no distinct dividing line between leukemia and pseudoleukemia as the term is applied by Sternberg. Among these authors, Sternberg as well as Borsch and Bante exclude from this classification of the lymphomatoses the granuloma-like tumor or Hodgkin's disease as an entirely different and distinct process. This is a view upheld by all the recent German investigators, as well as certain English and American writers. During the early and even more confused state of our knowledge concerning these conditions, it is probable that cases which would now be termed pseudoleukemia by continental writers were classed as Hodgkin's disease.

There is indeed still some question as to the existence of the condition which Sternberg terms pseudoleukemia, a disease resembling in every respect lymphatic leukemia, except for the lymphemia. It is well known that during the course of lymphatic leukemia there may be periods lasting weeks, months, or even years in which there is little or no rise in the total number of white cells of the blood, and at times scarcely any increase in the relative numbers of lymphocytes. During such stages the disease might readily be termed pseudoleukemia, or without a histological examination of the tumor masses might even be mistaken for Hodgkin's disease and it is probably to this class that the so-called transition cases from Hodgkin's disease to lymphatic leukemia belong.

In *lymphatic leukemia* the glandular enlargement may be well marked, but is absolutely uniform, practically all the glands in the body taking an equal part, a condition which may occur but is not usual in Hodgkin's disease. The spleen may be enormously enlarged, and since in many other respects this disease may simulate Hodgkin's disease, it may be extremely difficult to differentiate them without a blood examination. But a careful study of the blood will lead to a correct diagnosis.

Of all types of glandular enlargements the one most often mistaken for Hodgkin's disease is *tuberculosis*. Sometimes, indeed, from a clinical examination alone, it is impossible to tell the affections apart. There are two types of tuberculous adenitis to which particular attention must be paid. One of these is an acute tuberculosis, a comparatively rare form, which may affect the cervical lymph nodes and cause confusion in the diagnosis. In this condition the glands may swell rapidly. One or both sides of the neck may be involved. The enlargement generally begins in the nodes beneath the jaw and in the anterior triangle. As a rule, the nodes are painful or tender, and fever is present at some time. To palpation the tumors are regular, oval, fairly firm, but elastic. They may be readily outlined, separate, and freely movable beneath the skin; so that unless there is a recognizable tuberculous lesion elsewhere, which may give a clue as to the real nature of the lymph gland swelling, it is often very difficult to decide whether one has to deal with tuberculosis or Hodgkin's disease. Even after the tumors are removed the macro-

[1] *Zeit. f. klin. Med.*, 1904, lii, 285.

scopic appearance is at first deceiving. Microscopically the tissue is filled with typical miliary tubercles.

The second and common form of *tuberculous adenitis* which is so difficult to differentiate from Hodgkin's disease is the generalized caseous type. It is this variety which Fagge described. As a rule, in cases of extensive glandular tuberculosis there is a broken-down gland; or the larger tumors are matted together and immobile, while the smaller glands are hard, irregular, and form corded chains. A history may be obtained of glandular enlargement dating back several years, or the scar of a healed sinus discovered. But the class of cases which are so readily mistaken for Hodgkin's disease is different. This form of tuberculosis may imitate Hodgkin's disease almost exactly in its clinical course. The tumors may be very large, and present not only in the neck, but in the axillæ, mediastinum, and abdomen. They are hard, do not break down, often appear as separate masses, and are not attached to the skin. When removed the glands are found to be entirely caseous, with a narrow zone of connective tissue about the margin.

To establish the diagnosis in such cases the tuberculin test may be tried. Occasionally the *x*-rays will show in tuberculous glands shadows due to deposits of calcium salts or to actual calcification. These shadows when present are strong evidence of tuberculosis. But even more satisfactory is the removal of a gland for microscopic examination. By this method a diagnosis is arrived at with absolute certainty. Indeed, this method is by far the most satisfactory one to pursue in any doubtful case, and in many of the more obscure cases of glandular enlargement is absolutely essential for an accurate diagnosis. Since an accurate conclusion is not only highly desirable but often absolutely essential for prognosis and especially the correct treatment, the slight surgical procedure is more than justified.

Prognosis.—Hodgkin's disease is said to be fatal in every instance, and the patient rarely lives more than three to five years. Of 49 fatal cases, 34 died within two years. One patient lived six years and two lived seven years.

During the late stages of the disease the patient presents a pitiable condition. The tumors, perhaps in the neck or mediastinum or axilla, attain enormous proportions; there is cachexia and dyspnœa; the arms are wasted and the abdomen and legs often are swollen. Death may come, as in other wasting diseases, from a secondary infection; or may be mechanical and result from pressure of the tumors upon the trachea, giving rise to asphyxia. Occasionally œdema of the larynx ends the scene. Of the secondary infections, tuberculosis is by far the commonest. It is mentioned as a complication or as the immediate cause of death in 13 of the 86 cases, or in over 15 per cent. Occasionally the patient dies of miliary tuberculosis. General streptococcus infections, acute endocarditis, acute pleurisy, and peritonitis determine the lethal exit in a certain proportion. Rarely death seems to be dependent upon the severe secondary anemia.

Treatment.—Up to the present time neither medicinal nor operative treatment has been effectual in bringing about a cure of Hodgkin's disease.

Arsenic has been most generally employed. Following continuous doses of Fowler's solution the glands frequently diminish in size, but the improvement is only temporary and the tumors sooner or later return and proceed to enlarge. The results of operative treatment, which at one time was in vogue, have not proved of lasting benefit. Removal of a few enlarged glands is of no avail, and even when a complete dissection of the tumors is made there is inevitably a recurrence, if not at the site of the operation, at least in some other region. Repeated operations have not proved successful. Not infrequently after an operation the glands return in increased numbers, and grow with greater rapidity than before. Recently Billings and Rosenow have reported great improvement after treatment with a vaccine prepared from the diphtheroid bacillus cultivated from the lymph nodes. In most cases this method was combined with the use of *x*-rays.

The use of the *x*-rays, particularly in the hands of certain clinicians, has proved of more benefit and offered more hope than any other method of treatment. Schirmer,[1] in 1905, collected reports of 21 cases of pseudoleukemia, and again, in 1906,[2] added 19 more cases to the list, making in all 40 cases. The patients were exposed to the action of the rays over a time lasting from six to eleven months. The immediate results are almost always satisfactory. The tumors shrink away or disappear entirely, sometimes with surprising rapidity, but when the treatment is discontinued the growths return and require a second course of treatment. Pancoast[3] has collected 44 cases from the literature, and finds that although the *x*-ray treatment has not, so far, effected a cure, it does prolong the life of the patient. Of 29 of the 44 cases in which final reports have been received, 24.1 per cent. have lived for from three to four years after the first symptomatic cure. Still later reports are even more encouraging.

The manner in which the *x*-rays act upon the glands in Hodgkin's disease is made clear by a series of experiments which Heineke[4] performed upon animals. He found that when guinea-pigs and white mice are exposed to the action of the *x*-rays all the lymphoid tissue of the body is very rapidly destroyed. In the lymph glands the small lymphocytes show chromatolysis, and if the exposure is continued for a sufficient length of time the lymphocytes rapidly disappear. And since cells other than lymphocytes are left unharmed, this action of the *x*-rays is, to a certain degree, specific. The destructive action is, however, not permanent. After the exposures have been discontinued, lymphocytes reappear and lymph glands regenerate. Warthin,[5] in a similar series of experiments, obtained practically the same results. Heineke found, moreover, that not all cases of Hodgkin's disease respond with the same alacrity to the treatment by the *x*-rays. This difference he considers is due to a difference in the structure of the glands. Tumors of

[1] *Cent. f. d. Grenzg. der Med. und Chir.*, 1905, viii, 31, 56, 98.
[2] *Ibid.*, 1906, ix, 561, 609.
[3] *University of Pennsylvania Medical Bulletin*, 1907, xix, 282.
[4] *Mitth. aus der Grenzgebiete der Med. u. Chir.*, 1904, Band xiv, Heft 1 and 2; *Deut. Zeit. f. Chir.*, 1905, lxxviii, 196.
[5] *International Clinics*, 1906, iv, 243.

the soft type, which are cellular, and in which most of the cells are lymphoid cells, disappear rapidly after exposure to *x*-rays, while tumors of the hard type, in which the growth is composed principally of connective tissue, are scarcely, if at all, influenced. Unfortunately, no cure is known for this terrible disease, but at least we have a method of prolonging life and perhaps for combating the secondary pressure symptoms which are looked upon with so much dread.

PART IV.

DISEASES OF THE DUCTLESS GLANDS.

CHAPTER XX.

DISEASES OF THE ADRENAL GLANDS.

By GEORGE DOCK, M.D.

The adrenal glands, discovered by Eustachius in 1564, did not acquire importance until Addison's work (1855) on the disease that now bears his name. The adrenals are composed of two parts, as shown by Kölliker, the cortex and medulla. The cortex measures from 0.28 to 1.12 mm. in thickness; the medulla, 0.35 to 0.75 mm. in the periphery, from 2 to 3.3 mm. in the inner part. The glands are smaller in advanced age. Negroes are said to have larger ones than Caucasians. The weight of the glands varies from 4.8 to 7.3 grams, depending partly on the amount of blood.

The blood supply is large and is noteworthy from the fact that the same blood circulates through both cortex and medulla, and partly in a cavernous system, so that it is separated from the cells of the gland, in many places only by an endothelial layer. According to Manasse and others, even this layer is absent in some places. The lymphatics are numerous.

Many nerves enter the adrenals, thirty-three on the right side, according to Kölliker, medullated and non-medullated. They are derived from the semilunar ganglion, renal plexus, splanchnic, and vagus. Their branches pass between the cylinders of cortical cells and ramify closely among the cells of the medulla.

Development.—The cortex of the adrenals develops in the "inter-renal zone" of the cœlom-epithelium (Wolffian body). Remains of the inter-renal buds give rise to accessory adrenals, including those of Marchand.

The Chromaffin Tissue.—The medulla develops from the anlage of the sympathetic ganglia. Until recently it was looked upon as either nervous or of cortical origin, but the investigations of A. Kohn[1] (1898 and later), Wiesel, Biedl, and others put the sympathetic origin beyond doubt.

[1] Of Kohn's numerous articles, it is enough to refer to the following, where other references may be found: "Das chromaffine Gewebe," *Ergebnisse der Anat. und Entwickelungsgeschichte* (Merkel-Bonnet), Band xii, 1902–1903; "Die Paraganglien," *Archiv f. mik. Anat.*, Band lxii. See also Wiesel, "The Anatomy, Physiology, and Pathology of the Chromaffin System, etc.," *International Clinics*, 1905, vol. ii, 15th series, p. 288.

From the researches made by and stimulated by Kohn, it appears that the medulla of the adrenals is the most extensive collection of "chromaffin tissue," a cellular material rich in vessels and nerves, and including as its most important constituents the "chromaffin cells." The cells are characterized by their intense yellow or brown reaction with chromic salts (Henle, 1841; Stilling, 1890). Stilling's term "chromophile" tends to error, as it is used also in connection with reactions to dyes; Poll's more accurate name, "phæochrome" (φαιός, brown) does not seem likely to be adopted. "The chromaffin tissue has the same histological arrangement in different parts of the same individual and in different classes of vertebrates. It presents a characteristic cell type in all vertebrates so far examined. It has in all organs and in various animals the same histogenesis—the sympathetic. Its extracts, so far as they have been examined, have the same physiological action."[1] Small or large groups of such cells are found on the sympathetic nerves, "from the neck to the coccyx," in the ganglia, and on and in the great vessels. To independent groups of the tissue Kohn gives the name of "chromaffin bodies" or "paraganglia." These appear as roundish or elongated bodies, with connective tissue capsules, and provided with nerves, and very richly with bloodvessels. The medulla of the adrenals is the largest collection of such tissue. Others are the carotid and (probably) the coccygeal glands and "Zuckerkandl's organ." Wiesel also describes the same tissue in the hypophysis. Much of the chromaffin tissue undergoes atrophy in fetal life, but Wiesel found chromaffin cells in the sympathetic of old people. Aschoff and Kohn think that many so-called "accessory adrenals" have really been chromaffin tissue.

Accessory adrenals, made up of cortical tissue and resembling the zona fasciculata of the cortex in structure, are of frequent occurrence, being found in almost all bodies examined (less frequently in advanced age), from the liver to the genital organs. Their number varies in different animals. True accessory adrenals, containing cortex and medulla, are rare, but sometimes occur in the solar plexus, less frequently in other parts. In some cases in which medullary tissue has been claimed to occur, as in certain adrenals of Marchand, Aschoff thinks postmortem changes had led to error. Wiesel would limit the name accessory adrenals to bodies of cortical structure, and looks upon the others as "chromaffin bodies."

The importance of such a system of tissue in pathology is obvious, and the necessity of taking it into consideration in suspected cases of adrenal disease is imperative.

Physiology.—Many details of the physiology of the adrenals are still unknown or contradictory. Early experiments showed the vital necessity of the glands, and this has been confirmed by later observers with superior technical methods. The existence of a blood-pressure raising substance was shown by early observers, and this was isolated by Abel (epinephrin) and Fuerth (suprarenin), and later, in pure form, by Takamine and Aldrich. With the preparation best known, adrenalin,

[1] Gierke, "Chromaffines System und seine Pathologie," *Ergebnisse der allg. Path.*, 1904–1905, Jahrg. x, p. 502 et seq.

an enormous amount of chemical and physiological work has been done. Only an outline can be given here, and I follow the summary of Biedl, whose text and bibliography must be consulted by all who undertake a fuller knowledge of the subject.[1]

The adrenals are typical glands of internal secretion, called also endocrinous glands, though the cells differ in origin from those of other secreting organs. Adrenalin has been imitated synthetically (Stolz); it is an orthodioxyphenyl-ethanol-methylamine. It is formed in the cells of the chromaffin tissue, of which the adrenal medulla is a minor part, and enters the venous blood, from which it reaches all parts of the body. According to Biedl, 4.3 mg. are produced in twenty-four hours, giving a proportion of about one-half millionth in the blood. The secretion is a hormone, and exerts an effect on all tissues innervated by the sympathetic system. Among the most important functions under the influence of the chromaffin tissue are the following: Stimulation of tonicity of the heart and bloodvessels, narrowing peripheral vessels and raising blood pressure, but dilating the coronary arteries; usually also slowing the pulse, followed by increased frequency; quieting of respiration; relaxation of stomach and intestine, but with contraction of the pylorus, ileocecal valve and anal sphincter; excitation or inhibition of uterine muscle, according to the fibres affected (Falta and Fleming); diuresis, by action on the renal vessels; salivation, and in large doses, sweating. Adrenalin also causes hyperglycemia and glycosuria, shown by F. Blum and others; increases the breakdown of proteins in the body and the respiratory metabolism; sometimes causes increase of temperature; increases neutrophile leukocytes in the blood and causes eosinophiles to disappear; it may lead to polycythemia by driving plasma from the blood (Bertelli, Falta and Schweeger).

Adrenalin can be demonstrated in the first half of fetal life (Langlois and Rehns); it is diminished by muscular exercise, narcosis, and starvation; it has a close relation to kidney disease, hyperplasia of chromaffin tissue being a common finding in such cases; it increases in amount from birth to the tenth year and then remains fairly constant; it is diminished in certain acute diseases, especially diphtheria; also in Addison's disease, and is absent from the tissues of hypernephromata.

The functions of the adrenal cortex have been relatively neglected since the discovery of adrenalin, but renewed attention has been directed to it. Its richness in important chemical bodies, such as cholin, oxydase, and lipoid is suggestive. Gautrelet has set up the theory of a cholinogen system as an antagonistic regulator to adrenalin. The lipoid has been supposed to have a relation to the hypothetic detoxicating action of the adrenals—a function thought to exist not only toward endogenous, but also exogenous poisons. The relations to growth and sexual characteristics are mentioned under tumors.

Relation of Disordered Adrenal Function to Disease.—Certain tendencies in contemporary literature may be noticed. Bernard and Bigart suggest the terms "hyperepinephry" and "hypo-epinephry," to distinguish

[1] Biedle, Artur, Innere Sekretion. Ihre physiologischen Orundlagen und ihre Bedeutung fur die Pathologie. 2. neubearbeitete Auflage, 1913.

clinical features due respectively to excess or deficiency of adrenal function and including the possibility of relative excess or deficiency from the abnormal amount or character of antagonizing secretions. Hypoepinephry or adrenal inadequacy is distinguished from Addison's disease by the absence of pigmentation. Hyperepinephry is impossible at present to distinguish from other cases of high arterial tension. Vaquez's idea of the adrenal origin of hypertension makes the distinction superfluous, if we can only exclude all other causes of high tension, but the evidence at present is conflicting.

Hypo-epinephry, adrenal inadequacy, is easier to circumscribe, at least theoretically, and occurs in three chief forms, acute, subacute, and chronic. The former includes the "pseudomeningitic" form of Ebstein, the "pseudocholeraic" form, and "pseudomeningitic" form of Sergent. The subacute forms last from a few weeks to a few months; the chronic cases are equivalent to so-called partial Addison's disease. The essential features are myasthenia and hypotension, the systolic pressure usually being below 100 mm. of mercury. Other symptoms are: Hyperesthesias, pains in the lumbar region or elsewhere, headache, delirium and coma, digestive disturbances, sudden death, with or without previous symptoms. Riesman[1] advises treatment with adrenal extract, 5 grs., two to three times daily. Sergent[2] describes a vasomotor phenomenon which he calls the "white line," a pale area appearing in one-half to one minute after scratching the skin, and lasting for several minutes. Le Clerc denies its value. Dufour and Rogues,[3] Fursac and Schneider[4] give hypo-epinephry an important rôle in the production of neurasthenia, others ascribe to it the low arterial pressure of cirrhosis of the liver (Ferrannini), or the nervous symptoms of movable kidney (Championniére). The future must show the real relations.

There are many evidences of a close relation between the adrenals and various other ductless glands. Animal experiments show a relation between the sexual organs and the adrenals. Marchand's case of feminine hermaphroditism with atrophy of the ovaries and hyperplasia of the adrenals, and Bossi's case of osteomalacia improved by adrenalin are cited to confirm this. Hypertrophy of the adrenals occurs in pregnancy, and there are cyclic changes parallel to those of sexual function in guinea-pigs (Kolmer). Hypertrophy also occurs after castration. Many examples of a relation between growth and the adrenals have been published, especially the celebrated case of Linser, in which a boy aged five and one-half years, with hypernephroma, resembled one of sixteen to eighteen years. Other examples will be mentioned under Anomalies.

Such facts as the pigmentation of Basedow's disease and the coincidence of that with adrenal disease suggest the relation of the adrenals and the thyroid. Pansini and Benenati saw a case in which there was tuberculosis of both adrenals, Addison's disease, enlargement of the once atrophied thymus, hypertrophy of the thyroid, pituitary, and spleen. Persistence

[1] *Journal of the American Medical Association*, 1912, lviii, 1846.
[2] *Presse Médicale*, November 15, 1903.
[3] *Archives générales*, 1904, p. 1533.
[4] *Rev. de Méd.*, 1907, p. 970.

of the thymus has probably been too little recognized in many cases hitherto examined, so that it can hardly be discussed at present. The resemblance of the structure of the hypophysis and adrenal and the occurrence of chromaffin tissue in the former lead to the view of a close relation here.[1]

ANOMALIES OF THE ADRENALS.

Absence of the adrenals has been noted, but at a time when no attention was paid to possible compensating adrenal tissue. *Hyperplasia* of the cortex was seen by Marchand in a case of defective development of the genitals, with accessory adrenal in the broad ligament.

Hypoplasia has been noted, and is important on account of its relations. It has been found with hemicephaly and other failures of development of the brain, with retarded sexual development, osteogenesis imperfecta, and osteomalacia. Czerny has seen absence of the medulla in 5 cases of hydrocephalus; Hansemann, 8 cases of anencephaly with atrophy. Wiesel observed hypoplasia of the chromaffin system with hypoplasia of the vascular system and other changes, and in one case status thymicus and sudden death with hypoplasia of the medulla of the adrenals, and also once in a fatal case of sunstroke. Carl Hart found the adrenals enlarged in animals injected with the juice of a persistent thymus.

It is noteworthy that in cases of movable kidney the adrenals remain in the normal position. In cases of renal tumor they are sometimes displaced. Anomalies of position are rare. Pilliet found the right adrenal under the fibrous capsule of the kidney. Horseshoe adrenals have been seen (Orth).

Compensatory hypertrophy of an adrenal gland has often been observed in case of disease (Durst, Simmonds) or faulty development of the other. Neusser states that both cortex and medulla are affected; Karakascheff found only the cortex hypertrophied, as appears to be the case in experiments on animals. In a case of tuberculosis of both adrenals, Wiesel found hypertrophy of chromaffin tissue outside the adrenals, especially in large amounts on the solar plexus.

In future the finding of anomalies of the adrenals should lead at once to the careful examination of the whole chromaffin system, as well as to the search for cortical adrenals and the examination of the other ductless glands.

INFECTIONS AND INTOXICATIONS.

These affect the adrenals sometimes alone, sometimes along with other organs, in varying degrees of intensity. The anatomical changes in such cases are either congestion, hemorrhage, or infiltration. Such changes

[1] H. D. Rolleston, "Some Problems in Connection with the Suprarenals," *The Lancet*, September 28, 1907, ii. C. E. de M. Sajous, *The Internal Secretions and the Principles of Medicine*, 1903, 1907. L. Bernard, "Du role des glandes surrénales dans les états pathologiques," *Revue de Méd.*, October 10, 1907, p. 977. Eppinger, Falta, and Rudinger, "Ueber die Wechselwirkung der Drüsen mit innerer Sekretion," *Zeitschrift f. klin. Med.*, 1908, Band lxvi, pp. 1 to 200. Biedl, Innere Sekretion, 1913. W. Falta, Die Erkrankungen der Blutdrusen, 1913. M. Lewandowsky, Ed., *Handbuch der Neurologie*, 1913, Band iv. D. Noel Paton, *The Nervous and Chemical Regulators of Metabolism*, 1913.

are found in experimental diphtheria, tetanus, anthrax, pneumonia, etc. In rabies, on the contrary, reactive processes were found by Morchini, Langlois, and Lubarsch, and Elliott and Tuckett found that in cases of infection of the glands the adrenalin was diminished. An antitoxic action, if present, does not coincide with increased blood pressure raising function, but the reverse. "There is no proof that the adrenals play a part in the defence of the organism against infection" (Bernard). In men Oppenheim and Loeper found lesions similar to those in experiments on animals. The effect upon the symptom complex in such cases is, of course, impossible to determine with our present methods. In some cases the loss of adrenalin may be suspected, as in a case of Sergent, in which a man with pneumonia and marked depression had hemorrhagic inflammation in both adrenals. Sicard made a diagnosis of adrenal insufficiency in a case of bronchopneumonia with extreme asthenia, diarrhœa, low temperature, and blood pressure 7.8 by Potain's sphygmomanometer, in which adrenal hemorrhages were found.

Intoxications also affect the adrenals. The action of mercury is unsettled. In lead poisoning, which causes hyperepinephry in guinea-pigs (Bernard and Bigart), Gouget thinks the atheroma is brought about by the agency of adrenalin. In a case of lead encephalopathy, however, Ménétrier found the adrenals normal and no atheroma of the aorta. Biliary intoxication causes congestion and hemorrhage, stimulation of the cells in acute cases, depression in chronic ones (Bernard and Bigart). The melanoderma, low blood pressure, and asthenia of jaundice might be explained in this way (Gilbert and Lereboullet, Gaudy, Gourand). Renal auto-intoxication has often been looked upon as a potent cause of adrenal disease. Bernard describes a cortical hyperplasia of the adrenals with renal disease, but does not think it the cause of high blood pressure.

CIRCULATORY DISTURBANCES OF THE ADRENALS.

Anemia of the adrenals is of no clinical significance, and the same is true of anemic necrosis.

Hyperemia is frequent, especially the passive form, as a result of disease of the heart and lungs. Active hyperemia occurs in infections, especially diphtheria, typhoid fever, pneumonia, erysipelas, and smallpox. Both of these forms are likely to be associated with hemorrhages. The latter may also be caused by trauma, by blood conditions such as leukemia and hemorrhagic diathesis, thrombosis, and embolism. It is common in stillborn children, and has been attributed to efforts at resuscitation. Males are affected oftener than females.

Hemorrhages may be capillary and punctate, few or many, and may be of any size, even up to that of a man's head. They are unilateral or bilateral, the right side being more often affected than the left. The blood undergoes the usual changes, and the reaction around the focus varies with the amount of blood and the conditions associated with the hemorrhage. In cases with recovery absorption and calcification occur, with more of less fibrous tissue in the vicinity.

Symptoms.—Virchow, who first called attention to the subject, described severe symptoms of the typhoid state, and signs of peritoneal irritation and convulsions, soon fatal. Karakascheff emphasized asthenia and intestinal irritation. In Munson's[1] case myasthenia was not specially marked. According to Rolleston the most characteristic symptoms are: "Sudden onset with fever, violent pain in the hypochondrium radiating to the loins, convulsions, vomiting, diarrhœa, and later tympanites, collapse, and death within forty-eight hours from the onset." Some of the phenomena are doubtless due to damage to the abdominal sympathetic, producing symptoms like those of hemorrhagic pancreatitis or ileus. Purpura sometimes occurs, especially in children, along with fever and convulsions, suggesting an acute exanthem (Munson), and it has been suggested (Dudgeon[2]) that purpura is the expression of acute destruction of adrenals, as pigmentation is of the chronic kind. Arnaud describes a group of cases without bronzing of the skin, but with other evidences of chronic inadequacy of the adrenals.[3]

INFLAMMATION OR SOFTENING OF THE ADRENALS.

Various forms of inflammation of the adrenals have long been described, but the subject has acquired a new importance from work instigated by Lubarsch. It will be remembered that the name of "suprarenal capsule" was given because of the frequent presence of a cavity in the organ. At a later period, this was looked upon as the result of portmortem softening, without distinct pathological relations. Lubarsch was impressed by the fact that the change was not parallel to other postmortem alterations, and at his suggestion E. Rosenstein[4] made an investigation, as the result of which he came to the following conclusions:

"Softening and cavity formation of the suprarenal glands is not a pure postmortem phenomenon, due to decomposition. As a rule, disturbances of circulation, especially acute inflammatory conditions at the boundary of the cortex and medulla, prepare the way for the softening. Inflammatory changes of the suprarenal glands are much more frequent than is usually supposed, and appear both as exudative and productive processes. Most lung diseases, especially tuberculosis and pneumonia, advanced arteriosclerosis and heart disease—in short, diseases prone to abdominal engorgement—favor the process, while in anemia, including pernicious anemia and amyloid disease, the suprarenals are intact. The cavity formation occurs equally on both sides (and so cannot be due to bile imbibition) as small or large cavities, visible at once on sectioning or upon slight pressure. The cavities may be found from six to fourteen hours postmortem, the usual time for making the autopsies, but cavities are indicated two and one-half hours after death. Macroscopically, the medulla is wholly or partly absent in case of large cavities, the cortex

[1] *Journal of the American Medical Association*, July 6, 1907, p. 19.
[2] *American Journal of the Medical Sciences*, 1904, cxxvii, 134.
[3] See the excellent study of R. S. Lavenson, "Acute Insufficiency of the Suprarenals," *Archives of Internal Medicine*, 1908, vol. ii.
[4] *Arbeiten aus den path. anat. Abth. der K. hyg. Inst. zu Posen*, 1901, p. 116.

narrower than normal. Microscopic examination shows ragged walls formed of normal medulla or cortex. The veins remain, passing through the cavities. Inflammatory changes are not always present, but their frequency in cases in which cavities are found early seems to point to a relation."

Abscesses are found in the adrenals in cases of inflammation in the vicinity or in septicopyemia, rarely primary, as in the remarkable case of Janowski.[1] In this, weak pulse and heart and dark brown urine were striking symptoms. When the inflammatory process is limited in size, healing occurs, with more or less scar tissue.

Symptoms.—The symptoms of acute inflammation are at present impossible to distinguish from those caused by other processes in the primary diseases. Asthenia, subnormal temperature, low blood pressure, and sudden death do not usually permit a diagnosis of adrenal involvement, although in some cases the course of the symptoms may enable a probable diagnosis to be made. In chronic inflammation with cirrhosis, the syndrome of Addison is present.[2]

TUMORS OF THE ADRENALS.

Hypernephroma.—The adrenals, like the kidneys and other parts of the urogenital tract, are often the seat of neoplasms, usually small, fatty looking, with a fibrous capsule and the microscopic structure of the cortex of the adrenals in most cases, although medullary hypernephromas have been described (Manasse, Berdez). They have been called adenoma, or adrenal struma, but hypernephroma is preferable. For the most part they are benign and discovered by accident at autopsy. Warthin[3] has reported a case in which, with adenomas of both adrenals, there was degeneration of the adrenals of Marchand. They may set up metastases without giving evidence of local malignancy, or the latter may occur, causing large tumors of marked peripheral growth, invading neighboring organs, including bloodvessels.

Malignant Tumors.—Malignant tumors of the adrenals have been described under the names of carcinoma and sarcoma. Morphologically both forms occur, and may pass into each other, or one with carcinoma structure may have sarcomatous metastases. The pathology of these growths has been the subject of much investigation, which is well utilized in the study of Woolley,[4] who prefers the term mesothelioma to any of the other names. A good many tumors of the chromaffin tissue, in the adrenals as well as elsewhere, have been reported. They have been called peritheliomas, gliomas, sarcomas, etc. In all such cases the chromic acid reaction should be used to determine the specific character of the cells. Rolleston and Mulon have called attention to the resemblance of adrenal cortical cells to "luteal cells."

All the malignant tumors of the adrenal are remarkable for their high

[1] *The Lancet*, July 23, 1898. [2] See E. Sergent, *Archives gén. de méd.*, 1904, p. 14.
[3] *Archives of Pediatrics*, 1901.
[4] *Transactions of the Association of American Physicians*, 1902.

degree of vascularity and their tendency to fatty degeneration. The combination predisposes them to hemorrhage, and they often form large cysts—nine pints of fluid were removed from one by McCosh—with contents more or less degenerated, formerly spoken of as "hemorrhagic cystic adrenal struma" (Henschen[1]).

Symptoms.—The symptoms of adrenal tumor are of great variety. According to Cooper, tumors of the right adrenal frequently press upon the cava; those of the left are in relation to the stomach. Cortical hypernephromas have a tendency to metastasis in certain localities, as the vertebræ, skull, head of the femur, clavicles, and brain.

R. Hutchison[2] has called attention to cases of sarcoma of the adrenals with metastases in the skull, ribs, sternum, and vertebræ, but not in the long bones (?), with proptosis, discoloration of eyelids, severe secondary anemia, without leukocytosis or signs of increased intracranial pressure, and running a rapid course. The histological type may not be fixed. Some of the tumors may have been hypernephromas. In some cases of hypernephroma symptoms of Addison's disease have been observed. In some cases the symptoms have improved after operation (Bittorf). It is possible that the symptoms are due not to secretions, but to the toxic substances liberated by the breaking down of the tumors. Neusser has thought that in some cases of adrenal tumors there was hypersecretion. The relations of adrenal tumors to growth and the secondary sexual characteristics are remarkable. Ernest E. Glynn[3] has analyzed the recorded cases, 17 in number, to which Jump, Beates and Babcock add another.[4] Females predominate, in the proportion of 14 to 3. If young, they acquire male sex characters, but the converse does not happen in boys, who, however, tend to precocity. Apert has ascribed the syndrome of hirsutism to hyperplasia and tumors of the adrenals. The syndrome is characterized by precocious growth, disturbances in the sexual sphere, obesity, and excess and anomalous growth of hair. If it occurs early, the result is pseudohermaphroditism or precocity (sexual); if late, obesity and hirsutism, sometimes of the reverse type. It is possible an opposite condition may cause senile nanism of Variot, progeria of Hastings Gilford or geromorphism of Charcot.

Diagnosis.—The diagnosis of adrenal tumors is often difficult. They are generally mistaken for renal tumors. H. Morris points out as useful signs their mobility, rapid growth, and the tendency to varicocele on the same side. The tumors often press upward. Israel[5] describes five groups. In the first there is no tumor, no symptoms of adrenal disease, but metastases. In the second, no tumor, but signs of adrenal disease, such as hematuria, paroxysmal pains, and paresthesias in the region of the lumbar plexus or the tenth dorsal nerve. In the third group there is a palpable tumor, but the kidney cannot also be palpated. In the fourth, both tumor and kidney are palpable. In the fifth group both organs have

[1] *Beiträge zur klin. Chirurgie*, 1906, vol. xlix.
[2] *Quarterly Journal of Medicine*, 1907, i, 33. See also the valuable article by Tileston and Wolbach, *Amer. Jour. Med. Sci.*, 1908, cxxxv, 871.
[3] *Quarterly Journal of Medicine*, 1911–12, v, 157.
[4] *Amer. Jour. Med Sci.*, 1914, cxlvii, 568.
[5] *Deutsche med. Woch.*, 1904, No. 44.

grown together. Fever is an important symptom, occurring in 50 per cent. of cases. As the case of Schittenhelm shows, the pulse may not suggest the condition, and severe symptoms may come on late and suddenly. Tumors of aberrant adrenal tissue present symptoms according to their location chiefly. Those in the kidney and liver are clinically most important.

Prognosis.—The prognosis of adrenal tumors is bad, largely on account of the late diagnosis, rapid growth, and tendency to metastasis.

TUBERCULOSIS OF THE ADRENALS.

Tuberculosis of the adrenals is especially important on account of the relations to Addison's disease, but its general features may be mentioned here. Miliary tuberculosis is less frequent than the diffuse or nodular and caseating forms. Either form may affect one or both adrenals. Men are more often affected than women; the ages from thirty to sixty are especially concerned. The infection is usually secondary, from tuberculosis of the lungs, bronchial glands, intestines, genital organs, kidney, or vertebræ. It is sometimes primary, and may set up miliary tuberculosis. More frequently groups or single miliary tubercles in any part of the gland caseate and undergo fibrous degeneration, which spreads into the adjacent tissue. Fresh tubercles may follow in crops, causing sometimes extensive changes in the neighboring organs. Tuberculosis of the peritoneum often follows. Amyloid degeneration is often present. Pigmentation of the skin is relatively rare, especially with one-sided lesions.

SYPHILIS OF THE ADRENALS.

Syphilis of the adrenals is rare, but has been seen in both congenital and acquired forms of the disease. Sclerosis usually follows. Addisonian symptoms are sometimes present.

ADDISON'S DISEASE.

Synonyms.—Bronzed skin disease. Melasma Addisonii seu suprarenale, morbus Addisonii (Lat.); asthénie surrénale, melanodermie asthénique, maladie bronzée, maladie d'Addison (Fr.); Addison'sche Krankheit (Germ.); morbo di Addison, malattia di Addison (It.); enfermedad de Addison ò bronceada (Sp.).

Definition.—Addison's disease is characterized clinically by pigmentation, muscular and vascular weakness, disturbances of the gastro-intestinal tract and nervous system, and other symptoms, and anatomically by disease of the adrenal glands.

Historical Note.—Although the occurrence of alterations in the adrenals was known before the time of Thomas Addison,[1] he not only gave so accurate a description of the clinical features of the disease that nothing essential has been changed, but also made a remarkably accurate attempt

[1] *On the Constitutional and Local Effects of Disease of the Suprarenal Capsules*, London, 1855; also in his "Published Writings," New Sydenham Society, 1868.

at defining its anatomical basis. It was, therefore, proper to give his name to the disease (Trousseau, 1856).

Pathogenesis.—Wilks and Greenhow very early emphasized the importance of the sympathetic nerve and Addison accepted it in part. As the relation of the sympathetic and the adrenals became clearer, the view became more prominent, and was well presented by von Neusser, who also saw beyond contemporary knowledge and was ready to grasp the significance of the discoveries in the chromaffin system. For a short time toxic and insufficiency theories of the adrenals dominated, but at present the views of Wiesel seem likely to prevail.[1] Wiesel believes that any part of the chromaffin system may be at fault, but in addition to disease of that tissue, he sees a constitutional predisposition, and looks upon the *status thymico-lymphaticus* as equal or almost equal to the chromaffin tissue in the pathogenesis of Addison's disease. He suggests that adrenal inadequacy prevents the involution of the thymus; the lymphatic glands undergo hyperplasia, the vascular and genital systems hypoplasia. The hitherto obscure cases of fibrosis of the adrenals fit in well with this theory, though the infectious and traumatic lesions of the chromaffin tissue, whether in the adrenals or in other parts of the system, may prove to lessen the importance of predisposition. It is no longer of any value to discuss the older cases of adrenal disease without Addison's symptoms or the latter without adrenal alterations, and in the future the method of examination pointed out by Wiesel must be followed. His method consists in the removal of almost the whole sympathetic system—the two adrenals, two chains of ganglia, the large thoracic, abdominal and pelvic plexuses, the hila of the kidneys and the surrounding fat and connective tissue in which chromaffin bodies and (cortical) adrenal tissue are found, and the tissue around the origin of the inferior mesenteric artery, containing Zuckerkandl's organ. The tissues, after naked-eye examination, are fixed in potassium bichromate and formalin solution, later bichromate solution alone. Frozen sections are made after fixing and examined for fat and lipochrome. Many sympathetic ganglia are cut in two, and one-half is hardened in 95 per cent. alcohol as a control to the bichromate sections.

It is important to examine the carotid gland, the absence of which is an important sign of chromaffin hypoplasia.

Pathology.—The Adrenal Glands.—In the great majority of cases there is a lesion of the adrenals. Lewin, in his analysis of the literature up to 1892, found the adrenals diseased in 88 per cent. and "healthy" in 12 per cent. In 28 per cent. of cases of adrenal disease he found no history of pigmentation. On account of the sources of the histories these figures have only a general application.

The most frequent change is tuberculosis, which usually affects both glands, sometimes only one. It occurs in the adrenal primarily in some cases (Marchand, Chvostek, and others), more frequently with tuberculosis of other parts of the body, especially the lungs, genito-urinary tract, bones, peritoneum, etc. The most frequent change is widespread

[1] Von Neusser und Wiesel, *Die Erkrankungen der Nebennieren*, Vienna, 1910.

or complete caseation, with tubercle bacilli still present, and softening, fibrosis, or calcification. Sometimes there are groups of tubercles in various stages of degeneration, in the cortex, medulla, or on the surface, and invading the adjacent tissues. Sometimes there are very few tubercles or their remains, but old and more or less widespread fibrosis or adhesions. In rare cases tuberculous tumors are found, up to 60 grams weight in one case (Alezais and Arnaud).

Next in importance to tuberculosis is atrophy, which has recently been carefully studied by Bittorf.[1] In most cases the process is a simple atrophy or chronic interstitial inflammation with retraction and destruction of the parenchyma, resembling sclerosis of other parenchymatous organs. In simple atrophy the glands are more or less diminished in size, and sometimes as thin as paper. The general shape may not be much altered, or the gland may be represented by a small mass of fat. The color varies; the consistency is rarely altered. One adrenal may be wholly absent, even to its afferent vessels. Microscopically, the tissue is absent in one or more layers, or there is fatty degeneration, atrophy, or necrosis. Sometimes alterations are few, the chief abnormality being aplasia. Inflammatory alterations are absent or slight, but lymphocyte foci sometimes occur. According to some observers these are normal features of the adrenal. The vessels are sometimes normal, in other cases wide, or narrow, or atrophic. The nerves and ganglia in the glands are sometimes well preserved, sometimes atrophic.

The inflammatory atrophy of the adrenals leads to retraction and induration, sometimes with widespread fibrosis of the surrounding tissue. One or both glands or part of one gland may be involved. Microscopically there is fibrous tissue in strands, among the cell columns, resembling the appearance of a cirrhotic liver. The cells show various forms of degeneration, and there are also lymphocyte or polynuclear foci. Both arteries and veins are often thickened, especially in the intima. In rare cases inflammatory processes, possibly traumatic, cause tumor-like enlargements.

Carcinoma has been observed with Addison's disease by several observers, also sarcoma, melanotic tumors, hypernephromas, and peritheliomas. Syphilis has been noted, usually in the form of gummas with caseation, fibrosis and infiltration of the adjacent structures. Other lesions are: Cavernous angioma, mycosis fungoides, and echinococcus.

Sympathetic System.—The solar plexus and semilunar ganglia, as well as the ganglia and nerves in the adrenals, are often the seats of alterations in Addison's disease. They may be atrophied from the pressure of tumors, affected by tuberculosis by extension or as part of a widespread invasion, or they may be involved in inflammatory processes.

Besides these changes, various others have been described, such as pigmentation atrophy, small-celled infiltration, vascular changes, and fibrosis of the ganglia and nerves. Edel found the solar plexus and semilunar ganglia embedded in a fibrous mass. Fleiner found degenera-

[1] *Die Pathologie der Nebennierren und der Morbus Addisonii*, Jena, 1908.

tive changes in the spinal ganglia, posterior roots, and cord, Miklassewski in the intervertebral ganglia. But in most cases the changes are not severe, and many investigators have found few or none. This corresponds to the negative results of all who have attempted to produce the disease by extirpation of the sympathetic ganglia. The changes in the chromaffin system are more or less extensive disappearance of tissue, in or outside of the adrenals.

Brain and Cord.—In the spinal cord degenerations of various columns, infiltrations, thickening of the bloodvessels, and changes in ganglion cells have been described, but they are not peculiar to Addison's disease and have no significance in most cases. In the brain, œdema and other common vascular alterations occur. Tuberculosis of the brain or meninges may be an accidental finding.

Thyroid Gland.—The thyroid gland has sometimes been the seat of alterations, usually diminution rather than enlargement.

Persistent thymus was first noted by Starr, and considered accidental. It is probably part of the anatomical basis of the disease. The tonsils and other lymphoid tissues in the throat and tongue are sometimes enlarged. The pituitary gland is not affected, except in cases of polyglandular disease, as described on page 818.

In tuberculous cases the lungs, bronchial and mediastinal glands, genito-urinary tract, and lymph glands are often involved. The lymphoid tissue in the spleen is often increased, the organ in general enlarged.

Heart.—The heart is often in a state of brown atrophy; arteriosclerosis is rarely present in a marked degree.

Stomach and Intestines.—The stomach and intestines frequently show such changes as are found in various diseases with the local symptoms that occur in Addison's disease. Congestion, increase of mucus, and ecchymoses are not uncommon. The Peyer's patches and lymphoid tissue in general are hyperplastic, sometimes ulcerated. Tuberculosis of the intestines sometimes occurs. Pigmentation of the peritoneum, noted by some authors, is not considered of importance. The same is true of pigmentation of the pia mater. Pigmentation of the mucosa of the intestine is probably rare in the extent described by Allchin.

Skin.—The pigmentation of the skin and mucous membranes has been the subject of very extensive investigations. Most observers look upon the pigmentation merely as an exaggeration of the normal process. The pigment is found in the cells of the rete Malpighii, sometimes in the corium. In the mucous membranes it occupies a similar position. Pförringer, in the skin, and von Kahlden, in the mucosa of the tongue, found pigment granules in the vessels and in the tissue, free or in blood cells. An origin from the blood, however, is denied by Nothnagel, von Kahlden, and others, and many believe, with Pansini and Benenati, that the pigment is formed by the cells of the rete Malpighii. It does not contain iron. Carnot looks upon the pigment as a toxic substance, under normal conditions destroyed by the adrenals. The cause of the pigmentation is still unsettled. Wiesel thinks it due to sympathetic disease; Bittorf, as also Falta, to adrenal disease; Falta thinks cortex as well as medulla may be at fault.

Etiology.—Addison's disease is rare in general. It affects all races, climate, and countries, but is thought to be more frequent in the white race and in Europe. It affects men somewhat oftener than women (6 to 4). The ages most affected are from 15 to 60. Cases sometimes occur in childhood, as early as the third year, and it may be congenital, as in a case reported by Osler; it has been seen as late as the eightieth year. From what was said of the pathology, it is clear that the causes sometimes assigned—malaria, alcoholism, cold, trauma, emotional strains, childbirth—may be admitted, but actual cases are rare in which they have a definite value. Tuberculosis and syphilis have their specific causes. The majority of cases come from the working classes, but others are by no means exempt. Heredity is obviously of little importance, but the disease has been seen in brothers (Tscirkoff, Andrewes), and in a mother and children.

Symptoms.—Clinical Features.—For the general picture of the disease it is impossible to improve upon the words of Addison: "The patient, in most of the cases I have seen, has been observed gradually to fall off in general health; he becomes languid and weak, indisposed to either bodily or mental exertion; the appetite is impaired or entirely lost; the whites of the eyes become pearly; the pulse small and feeble, or perhaps somewhat large, but excessively soft and compressible; the body wastes, without, however, presenting the dry and shrivelled skin and extreme emaciation usually attendant on protracted malignant disease; slight pain or uneasiness is from time to time referred to the region of the stomach, and there is occasionally actual vomiting, which in one instance was both urgent and distressing; and it is by no means uncommon for the patient to manifest indications of disturbed cerebral circulation.

"Notwithstanding these unequivocal signs of feeble circulation, anemia, and general prostration, neither the most diligent inquiry nor the most careful physical examination tend to throw the slightest gleam of light upon the precise nature of the patient's malady; nor do we succeed in fixing upon any special lesion as the cause of this gradual and extraordinary constitutional change.

"We may, indeed, suspect some malignant or strumous disease—we may be led to inquire into the condition of the so-called blood-making organs—but we discover no proof of organic change anywhere; no enlargement of spleen, thyroid, thymus, or lymphatic glands; no evidence of renal disease, of purpura, or previous exhausting diarrhœa, or ague, or any long-continued exposure to miasmatic influences; but with a greater or less manifestation of the symptoms already enumerated we discover a most remarkable and, so far as I know, characteristic discoloration taking place in the skin—sufficiently marked, indeed, as generally to have attracted the attention of the patient himself or of the patient's friends.

"This discoloration pervades the whole surface of the body, but is commonly most strongly manifested on the face, neck, superior extremities, penis, and scrotum, and in the flexures of the axillæ and around the navel.

"It may be said to present a dingy or smoky appearance, or various

tints or shades of deep amber or chestnut-brown; and in one instance the skin was so universally and so deeply darkened, that, but for the features the patient might have been mistaken for a mulatto.

"In some cases the discoloration occurs in patches, or perhaps, rather, certain parts are so much darker than others as to impart to the surface a mottled or somewhat checkered appearance; and in one instance there were, in the midst of this dark mottling, certain insular portions of the integument presenting a blanched or morbidly white appearance, either in consequence of these portions having remained altogether unaffected by the disease, and thereby contrasting strongly with the surrounding skin, or, as I believe, from an actual defect of coloring matter in these parts. Indeed, as will appear in the subsequent cases, this irregular distribution of pigment cells is by no means limited to the integument, but is occasionally also made manifest on some of the internal structures.

"We have seen it in the form of small black spots, beneath the peritoneum of the mesentery and omentum—a form which in one instance presented itself on the skin of the abdomen.

"This singular discoloration usually increases with the advance of the disease; the anemia, languor, failure of appetite, and feebleness of the heart become aggravated; a darkish streak usually appears on the commissure of the lips; the body wastes, but without the emaciation and dry, harsh condition of the surface so commonly observed in ordinary malignant diseases; the pulse becomes smaller and weaker; and without any special complaint of pain or uneasiness the patient at length gradually sinks and expires."

Some writers have attempted to describe stages in the course of the disease, but so variable and at the same time insidious is the course in general that it seems better to consider the symptoms in detail, with reference to their variations.

Asthenia.—In most cases, whether tuberculous or otherwise, the earliest symptom is an unusual tendency to fatigue on bodily or mental exertion. In the beginning this is not uniform, and even in the most distinct asthenic periods does not oblige the patient to take to bed nor does it describe the striking weakness that occurs later. By degrees the weakness and loss of energy become more marked. The patient loses all inclination to exertion, and may have periods in which it seems impossible to rise from the bed. This may last for many months before the other symptoms develop to an extent making diagnosis possible, although an intense asthenia should always raise the thought of Addison's disease.

Gastro-intestinal Symptoms.—Often absent, when they do occur these are of great diagnostic value. Sometimes the stomach is free from symptoms, or the appetite is even voracious; more frequently the appetite becomes capricious, meat being especially repugnant, or appetite fails. There is a feeling of fulness after eating, nausea, eructations, or pyrosis. Constipation is the rule in the early stages. Later, irregular attacks of vomiting and diarrhœa make their appearance. Pain in the epigastrium or hypochondrium, the lumbar or sacral region, sometimes occurs, and with the other symptoms suggests gastric crises. Tenesmus is some-

times present. In the later stages the appetite fails completely; vomiting is frequent, and with the diarrhœa hastens the loss of strength.

Pigmentation.—This may occur early, and be discovered by accident before the other symptoms have been clearly recognized. Early discovery is more likely if the pigmentation occurs in irregular patches without relation to parts ordinarily pigmented. When it occurs on the face, neck, and hands, the areolæ and genitals, it may reach advanced degrees without exciting comment, or it may even be looked upon as evidence of health. The parts usually exposed to light, then the areolæ, external genitals, axillæ, flexor surfaces of the joints, median line between umbilicus and pubes, are first and most affected. Parts pressed upon by clothing, prominences, as over the spinous processes and knuckles, become dark sooner or later. Pigmentation is sometimes absent where the skin is shaded by the hair, and Bernard mentions a case in which pigmentation was general except on exposed parts; in many cases the hairy scalp is also affected. Scars are sometimes pigmented, sometimes surrounded by a dark areola. The palms and soles are rarely pigmented, except in the folds. Thibierge and also Scheult have seen the negro skin make darker by the disease in the areas affected by Addison's disease.

The pigment varies in color in different cases. Addison was well aware of this, and the different names given to the color are not always the result of fancy. It may be from a pale brown to a deep brown, bronze, or chocolate, or from a pale, dirty gray to an almost sooty black. The color is often darker where counterirritation has been used, but the writer cannot agree with Trémolière that intense pigmentation after a poultice or plaster is evidence of a latent adrenal insufficiency. The pigment is never uniform, but may be almost so, except for the areas that are usually darker. On the other hand, it is often intensely dark in small areas, like common moles, and it is often interrupted by areas of vitiligo, as Addison pointed out. These are often overlooked or considered as normal, but the characteristic curved outlines permit them to be easily recognized, as well as the darker color at the margin. Pigmentation of the mucous membranes is almost the rule, occurring on the lips at the margin of the skin, on the tongue, buccal mucosa, gums, eyelids, especially the edges, and sometimes on the conjunctiva. Sometimes it spreads out from the angles of the mouth or eyelids in distinct streaks. It also occurs on the mucous membranes of the genitals. A continuous dark brown line on the gums, near the margin, is sometimes very striking. Generally the pigmentation of the mucous membranes is not diffuse, but occurs in spots or streaks. The nail bed and nails are sometimes pigmented, and the hair seems to have a darker tint, looking dirty or dusty.

Aside from the pigmentation, the skin, as a rule, is smooth and elastic. Itching is rare, unless from complicating disease. Sweating is sometimes excessive, and the skin sometimes has a disagreeable fish-like odor. As rare complications in the skin, roseola, purpura, molluscum contagiosum, furunculosis, prurigo, and psoriasis have been described.

The "white line" is a very striking sign when present and deserves

careful study. In a case seen by the writer with Dr. H. A. Freund, it came on slowly and remained many minutes, after scratching the skin, as a broad, chalky, white mark, but could be seen on uncovering the patient wherever a fold or wrinkle of the clothing had been in contact.

Nervous and Mental Symptoms.—The tendency to fatigue from mental and physical exertion has been mentioned. Besides this, a constant apathy often develops, and is sometimes associated with depression, insomnia, or rarely increased tendency to sleep. Yawning is a marked symptom in some cases. Loss of memory, delirium, dizziness, tinnitus, and muscæ volitantes occur at times. Headache is frequent and sometimes violent. Diminished sensibility, or paresthesia—formication or numbness—sometimes exists in the pigmented or leukodermic areas. In the later stages the asthenia reaches a striking degree. Although the patient may not look very ill, weakness is so intense as to make the slightest movement difficult or impossible. Syncope comes on with alarming ease, with or without nausea, vomiting, and cold perspiration, from exertion, a prolonged examination, a tuberculin injection, and sometimes from accidental or other pressure on the abdomen.

In some cases the mind is affected. There is loss of memory, or imbecility in various degrees, sometimes even dementia. Depression is more common than excitement, but restlessness and anxiety occur. Tremor and choreiform and epileptiform convulsions are rare. Weakness of the special senses, especially smell, taste, and hearing, is not uncommon.

Pain in the muscles and nerves is very severe in some cases, especially pain of a neuralgic character in the epigastrium and lumbar region, sometimes in the joints. The latter may be swollen (Ebstein), leading to the diagnosis of rheumatic arthritis. The reflexes show no characteristic change. They are often slow and weak.

Heart and Circulation.—Cardiac weakness is part of the picture of the disease. The heart beat and sounds are faint, the pulse small, soft, and usually slightly accelerated. Exertion is likely to bring on alarming dyspnœa and palpitation. Murmurs are not always present. The blood pressure is usually low, as has long been recognized by the touch; observations with the sphygmomanometer, first made by Charlewood Turner (1899) confirm it. In four cases personally observed the maximum systolic pressure was 110, 108, 85, and 82; minimum, 85, 75, 65, 60 respectively (Stanton instrument; 12 cm. band). The two cases with lowest pressure were seen only a few days before death. Janeway has reported a patient with a systolic pressure of 140. Grünbaum[1] uses the blood pressure and adrenal extract in diagnosis. In a suspected case, if the pressure is low, 3 grains of adrenal extract are given three times a day for three days by the mouth. A rise of more than 10 mm. makes adrenal insufficiency almost a certainty. The subject is thoroughly discussed by Parisot.[2]

The Blood.—Addison looked upon the disease as an anemia, a view shared by many others and sometimes held even at the present time. In most cases, however, until the latest stages, marked anemia is rare,

[1] *Practitioner*, August, 1907.
[2] Pression artérielle et glandes a sécrétion interne, Paris, 1908.

or, if present, can be explained by complications, such as tuberculosis or cancer of important organs, or severe gastro-intestinal disturbances. The skin and mucous membranes are sometimes pale, suggesting pernicious anemia, but in most cases pallor is not marked. Foersterling's case of bronze skin with pernicious anemia and without macroscopic changes in the adrenals seems questionable. The usual conditions are illustrated by four fatal cases in the writer's clinic. These had red blood counts of 4,240,000 to 5,676,000 cells per cmm. The hemoglobin was low in most cases—65, 82, 87, and 100 per cent. The leukocytes are not increased, as a rule, sometimes slightly diminished, and the differential count shows no constant change. Neusser looks upon increase of lymphocytes as a bad omen. Large and small lymphocytes vary in different cases, and the total lymphocyte count may exceed that of the polynuclears. High red cell count and hemoglobin are doubtless due in some cases to concentration from loss of fluid. Such cases have been carefully examined by Christomanos and Hamel, and the latter compares the condition to the combination of oligemia and concentration of the blood sometimes seen in tuberculosis.

Abdominal Organs.—Besides the symptoms above mentioned, referred to the abdomen, more severe phenomena sometimes occur, such as pain or tenderness, diffuse or localized, and with rigidity of the abdominal wall. These symptoms excite suspicion of peritonitis, and in some cases are, in fact, associated with tuberculosis of the peritoneum. Ebstein and Zaudy report cases, with vomiting, going on to collapse, in which the cause could not be found. In some cases the pains are paroxysmal, and suggest crises of tabes or lead colic, while gallstones and gastric ulcer are often simulated by peculiar localizations of the pain.

Digestive Disturbances.—In rare cases of Addison's disease the stomach and intestines present no marked abnormalities. In the majority of cases there is more or less disturbance. Eructations, hiccough, and vomiting are frequent. The vomiting may occur with or without taking food. Remissions and exacerbations of the gastric symptoms are characteristic, especially in the earlier stages. In the later stage, vomiting becomes severe and painful, and hastens the fatal end. Mucus, bile, and traces of blood may then occur in the vomitus. Examination of the stomach contents usually shows no marked abnormality until an advanced period, when low or absent hydrochloric acid, diminished peptic power, and excess of mucus are encountered.

Constipation and diarrhœa occur in different cases in almost equal proportions, but constipation is more frequent in the early stages. Diarrhœa is sometimes profuse, rarely painful. The stools in such cases show mucus in excess, rarely blood. Tuberculosis of the intestine does not always cause distinct symptoms.

The liver and biliary tract rarely show clinical anomalies, and then only as complications. The spleen is sometimes enlarged.

In women amenorrhœa is a frequent symptom. Other menstrual anomalies are accidental. Tuberculosis of the uterus, tubes, and ovaries occurs in some cases. In men impotence has been observed. Tuberculosis of the epididymis may be a complication.

Urinary Organs.—Changes in the urine are neither constant nor specific. The quantity is sometimes diminished, sometimes increased. The specific gravity is rather low than high, the coloring matter not always increased. Indican and other coloring matter may be in excess in some cases. The finding of taurocholic and hippuric acid, of neurin, etc., has had no recent confirmation. Falta, Eppinger and Rudinger found a high glucose tolerance, and no glycosuria after adrenalin. Porges found hyperglycemia, confirmed by Bernstein.

The metabolism is usually reduced, corresponding to the cachexia. Adrenal preparations affect the metabolic processes differently in the different cases.[1] Emaciation is slight, and there may be excess of abdominal fat, but loss of muscle tissue may involve considerable loss of weight.

The temperature, in the absence of complications, is apt to be subnormal. In rare cases hyperpyretic temperatures have been recorded, 111° F. according to Barlet and Lucas.

Varieties of the Disease.—There are many varieties of type, both as regards course and combinations of symptoms. Some cases are acute, ending within a few weeks from the first discovery of illness. Many such cases are really chronic, as may be discovered on careful inquiry. A sudden increase of weakness, or an acute attack on the part of the stomach or intestines, first reveals the alarming condition. As to the clinical picture, it is hardly necessary to point out the differences caused by a preponderance or absence of cardinal symptoms—asthenia, pigmentation, and gastro-intestinal disturbances—nor is there any advantage in speaking of cases as "incomplete" or "fruste." There are some differences, depending on the age of the patient. Children are prone to gastro-intestinal symptoms, with asthenia, but with little pain, and to run a rapid course.

Diagnosis.—In some cases the diagnosis of Addison's disease is of the utmost simplicity. It can be made positively when we get a definite history of asthenia, vomiting, constipation and diarrhœa, pain in the abdomen and back; when we find pigmentation of the skin and mucous membranes, and when we can exclude visceral disease or blood disease (pernicious anemia) that might account for a similar picture.

As the pigmentation is the most characteristic sign, it is well to consider its use and value in the diagnosis. The most extreme pigmentation, in a person known to have been light-skinned previously, is rarely seen except in Addison's disease. Difficulties occur in cases in which the pigmentation is not so severe, or in which other causes for such a change cannot be excluded, and in which the other symptoms are not marked or their description not sufficiently clear. Even if the pigmentation cannot be assigned to any other cause, it is well to reserve the diagnosis until other symptoms, such as asthenia, can be positively recognized.

The other possible causes of pigmentation should be carefully considered. Difficulty is often experienced in patients with weakness and gastro-intestinal symptoms, sometimes neurasthenic, sometimes anemic, by an unusual degree of pigmentation in areas normally pigmented—the

[1] Magnus-Levy, *Handbuch der Pathologie des Stoffwechsels*, 1907, Band ii, p. 352.

areolæ, especially in women who have borne children and in old people, the median line of the abdomen, the axillæ and genitals. A knowledge of the existence of such conditions, based on inspection, will lead one to seek other evidences before making a positive diagnosis. Certain dark-skinned races, Chinese, Japanese, and Armenians, often have general pigmentation, increased in the usual areas, requiring a similar reserve. In both classes careful examination of the mucous membranes should be repeatedly made. Among negroes and in the yellow race (Japanese, according to Baelz) many healthy people have brownish-gray or chocolate-colored spots on the lips, gums, and conjunctiva. In such cases the constitutional symptoms must be depended upon.

The pigmentation of pregnancy, not only on the areolæ, median line, and genitals, but also sometimes upon the face and neck, has been mistaken for that of Addison's disease, but careful examination, especially if repeated, can rarely leave any doubt as to the real condition.

Vagabond's disease, or a discoloration that occurs in people not actually vagabonds, from neglect, sometimes assisted by pediculi, simulates Addison's disease. The color is on the exposed parts, but the skin is rough and shows scratch marks, two signs rare in Addison's disease. The history, the absence of constitutional symptoms, or their explanation by other diseases, and the effects of bathing, care, and nourishment, usually make the diagnosis easy. Roughness of the skin also excludes the mistaking of acanthosis nigricans for Addison's disease. Pediculosis and itching skin diseases sometimes cause pigmentation, but in these the scratches and the discovery of parasites or itching lesions prevent serious doubt. Hitschmann's case of pediculosis with pigmentation of the mucous membranes is a rare anomaly.

The pigmentation of malaria may cause difficulty, but the history, the condition of the blood in acute or chronic cases of malaria—so different from that of Addison's disease in the early stages—and the associated symptoms should enable one to avoid error. The pigmentation of syphilis and of scurvy can also usually be properly assigned by careful attention to the history and examination. Basedow's disease sometimes has a pigmentation resembling that of Addison's disease, but the other symptoms of the former are so clear that the only question would be whether there was a combination of both diseases, a point to be settled only by thorough examination and prolonged observation. In a case observed by Chvostek the pigmentation disappeared with the recovery of the exophthalmic goitre. The pigmentation of arthritis deformans should not lead to the diagnosis of Addison's disease in the absence of other symptoms.

Neusser, who has so thoroughly studied the skin changes in pellagra, points out the possibility of error in cases of diffuse pigmentation following erythema in the former disease. The pigmentation is sometimes macular. The erythema occurs chiefly in spring and fall; the mucous membranes are pale or livid; there is usually an intense anemia, assisted in many cases by malaria and syphilis. Neusser found an increase of eosinophile cells in the blood and stools, and looks upon that as a useful point in diagnosis. The gastro-intestinal symptoms may be much alike

in both diseases, although bulimia is more frequent than anorexia in pellagra. Careful attention to all the signs should prevent confusion.

Cancer and tuberculosis, with pigmentation, may cause error. In these the weakness in the later stages may suggest the asthenia of Addison's disease, but is rarely so extreme. In either case the adrenals may be involved, or the chromaffin or sympathetic system. When diagnostic difficulty occurs from either cancer or tuberculosis, the patient is usually in a stage when the exact diagnosis is not of therapeutic interest. F. Schultze has reported pigmentation of the tongue in cancer, an interesting observation, but one that raises the question as to a mechanism similar to that in Addison's disease.

Benign tumors of the uterus and ovaries are sometimes associated with an intense diffuse pigmentation of the skin, which disappears on removal of the growths. Other tumors with pigmentation, pelvic, pseudoleukemia, melanosarcoma, can be recognized by care in the observation of other signs and symptoms. In cases with constitutional symptoms the possibility of adrenal involvement must be considered.

The pigmentation of bronze diabetes should be recognized by the enlargement of the liver and glycosuria. In marked cases the color of the skin is not as much like that of Addison's disease as it is like that from nitrate of silver. This latter pigmentation also is to be excluded by the history and the constitutional symptoms.

Arsenical pigmentation may at first glance suggest Addison's disease. The hypertrophic processes in the epidermis, as well as the history of arsenical medication, may prevent error in some cases, but in cases of chronic poisoning from wall-paper, food, or drink, the diagnosis may be very difficult. Neusser points out the difficulty of assigning the proper cause when a tuberculous patient, treated with arsenic, becomes pigmented.

Jaundice cannot easily be mistaken for the pigmentation of Addison's disease, but in the recovery from chronic jaundice, after the bile color has disappeared from the scleræ and the mouth and from the urine, the face and hands often show a brown color not unlike that in icterus. In such a case unless the history of previous icterus is clear, the diagnosis may present great difficulty. Gastro-intestinal symptoms may be described; weakness may exist. The absence of intense asthenia is important to notein such cases.

It is remarkable how many patients with vitiligo present themselves solely on account of the pigmentation associated with the leukoderma, and how often a diagnosis of Addison's disease is made in such cases. The recognition of the vitiligo should be easy, but it is necessary in all cases to exclude Addison's disease with vitiligo.

Pernicious anemia, with or without arsenical treatment, sometimes has a diffuse or patchy pigmentation like that in atypical cases of Addison's disease. It may also be complicated with vitiligo. The weakness of the heart and muscles and the preservation of the subcutaneous fat, the gastro-intestinal disturbances, and absence of cause for the symptoms make a differential diagnosis difficult in cases without marked blood changes, or, if the latter are present, the combination of both diseases

may be suspected. In case the mucous membranes are pigmented the diagnosis would be much more strongly warranted. Complete examination of the blood will put the diagnosis beyond doubt, and the possibility of the combination is then of scientific rather than practical interest.

In chronic interstitial nephritis in children Sawyer has observed a brownish discoloration of the skin resembling Addison's disease. Nothing abnormal was found in the adrenal bodies in cases examined postmortem. The differential diagnosis should present no great difficulty if the heart, arteries, and urine are examined.

Pigmentation of the mucous membrane is an important sign, but, like all others, is not infallible. In the first place, pigment spots occur in the mouth not only in some healthy individuals of dark-skinned races, but even in rare cases in Caucasians (Nothnagel, Eichhorst). On the other hand, pigmentation of the mucosa is absent in some cases of Addison's disease.

Even when pigmentation is marked and characteristic, a differential diagnosis is essential. When pigmentation is slight or atypical, we should suspect Addison's disease if there is marked or progressive loss of strength without emaciation, and without cause, or if there is tuberculosis. "The suspicion is strengthened if the patient is young (in other words, in cases in which obscure internal disease of a malignant kind is not likely to occur), if there is no profound anemia, and if symptoms of gastro-intestinal irritation (which seem to be of nervous origin and which do not appear to be due to local stomach disease, such as simple ulceration) and lumbar pains are also present. It must be remembered that marked loss of weight (due to loss of muscle, but not to loss of fat) does not exclude Addison's disease" (Bramwell[1]).

In cases with pigmentation and no other explanation, but without asthenia and gastro-intestinal symptoms, a positive diagnosis should not be given without careful investigation. In such cases the diagnostic injection of tuberculin may be cautiously used. In cases of Addison's disease even small doses of tuberculin may cause alarming symptoms. The conjunctival or cutaneous reactions could be used, but in all of these tests it is important to consider the possibility of latent foci of tuberculosis in other organs. A safer course would be to make a careful study of the blood pressure with and without adrenal preparations, and postpone tuberculin tests until the general condition is fairly well known.

The diagnosis of the anatomical condition, whether tuberculous, atrophic, or otherwise, cannot be made with accuracy, nor can the condition of the sympathetic, spinal nerves, etc., be safely included in the diagnosis. More complete studies of well-observed cases must be made before such diagnoses can be depended upon. The diagnosis of "adrenal insufficiency" in cases not well marked does not often seem of advantage. Such cases need careful investigation postmortem.

Prognosis.—Addison's disease is universally classed as a fatal affection; in fact, recoveries of genuine cases are so rare as to leave no other prognosis possible. And yet it must be recognized that if the primary lesion

[1] *Clinical Studies*, 1904, ii, 257.

heals, if compensation can occur by the hypertrophy of other tissue capable of the same function, and if no other essential tissue is involved, recovery is possible.

In general, the course is chronic, lasting from one to three or four years from the earliest recognizable symptoms. Longer durations, eight, ten, even twenty years, have been reported. The longest duration seems to occur in uncomplicated tuberculosis of the adrenals. Atrophy of the adrenals usually causes rapidly progressing cases. Remissions and relative improvement occur spontaneously in most chronic cases. The end is either slow and gradual, with death from exhaustion, or sudden, from diarrhœa, vomiting, fever, syncope from exertion, or with toxic symptoms not always possible to explain.

Treatment.—The manifold causes and complex pathology of Addison's disease do not permit a scientific therapy at present. We are obliged to depend upon more or less imperfect theories or an empirical treatment, both of which have been far from satisfactory. The clinical diagnosis can rarely include accurate knowledge either of etiology or of pathological anatomy. On the ground of probabilities we can assume that tuberculosis is the cause in most cases. Sometimes we may make this almost certain by the results of specific tests.

In very rare cases syphilis may be recognized as the cause. Atrophy and some cases of destruction or pressure from tumors will remain as stumbling blocks in practice. Moreover, even in cases with known etiology, we cannot determine the extent of the lesion in the adrenals, the implication of the other chromaffin tissue, the possible compensatory hypertrophy of accessory cortical tissue, or the involvement of sympathetic or spinal nerves.

There is need for more direct examinations of the local conditions. In cases of recognizable tumor an attempt at operation is certainly justified. From the bad prognosis in general, it would seem proper to explore, surgically, in doubtful cases. The difficulties, not to say dangers, of such operations seem at present almost too great to justify them, but with improvements in technique such as can confidently be expected this objection will not be so strong. Oestreich[1] has made an important contribution to the operative treatment of adrenal disease. A woman with general symptoms, but without bronze skin, had a tumor in the stomach region the size of a small apple. This was extirpated and found to be a tuberculous adrenal. Recovery followed. It does not seem rational, as some have done, to assert that this was not a case of adrenal inadequacy. The symptoms were not complete; the disease was one-sided; compensation might have followed the possible healing of the diseased gland. But to wait for such a process to heal spontaneously would seem almost as absurd as to leave a tuberculous appendix or Fallopian tube to a similar fate.

The spontaneous remissions and the rare cases of recovery have led to a complete denial of the efficacy of treatment. It has been said that cases reported as recovered were only functional. Skepticism is very

[1] *Zeitschr. f. klin. Med.*, 1897, xxxi, 123.

desirable in such matters, but it must be conceded that we cannot, especially in the early stages, draw the line, and it would be better to assist recovery of a functional inadequacy, if we can, than to follow a purely expectant treatment.

Two plans are available, the so-called causal, and the symptomatic treatment, to which may be added the etiological, applicable in syphilis and tuberculosis.

Adrenal Therapy.—The treatment by adrenal glands or their preparations is sometimes spoken of as "causal" or "substitution" therapy, but obviously with a set of processes very different from those present in the treatment of myxœdema with thyroid preparations. So, we can substitute the faulty or absent secretion of the adrenal medulla with glandular tissue, with other chromaffin tissue, or with adrenalin or its congeners. But even if we give cortex tissue or its extracts, we have no assurance that it will replace the function of the healthy cortex.

The method is as yet purely experimental. We do not know either the best preparation or the dosage. Various plans have been followed; all have given good results in some cases, and all have failed in a larger number. The active principle of the medulla may be expected to have a good effect upon the muscles, the heart, and probably the pigmentation. Such an effect has been seen in patients treated, and a very striking fact is the relapse that sometimes comes after the cessation of the remedy. In some cases lassitude disappears, the muscular weakness also. In one case (Langlois) ergographic tests showed normal conditions after six weeks' treatment. In some cases the pigmentation subsides rapidly, and returns even more rapidly on stopping treatment. On the other hand, bad results occur sometimes in the very beginning of treatment.

E. W. Adams analyzed 105 cases in 1903, and found that alarming or fatal results had followed in 7, no improvement in 49, improvement in 33, and great improvement ("cures") in 16. Since Adams' report, many more cases have been treated, but without a definite advance in the proportion of good results or in the knowledge of details of treatment. It is impossible to see, at present, any essential difference between the various preparations, but a longer experience may change this.

The fresh glands have been used raw or slightly cooked or dried (Glandulæ suprarenales siccæ, U. S. P.); also liquid extracts. Sheep glands are most commonly selected. Wiesel used chromaffin tissue from calves with good results, but the difficulties in obtaining such tissue make this an unimportant source. The dose of gland or extract given has varied considerably, up to six fresh glands a day or 5 to 20 grains of extract three times a day.

Adrenalin and similar active principles have been used hypodermically and by the mouth. The latter method is probably just as certain as the former, for as Oliver and Schaefer proved, stomach digestion does not destroy the active principle. A dose of 5 minims of the 1 to 1000 solution can be given three times a day in the beginning, and increased, according to the effect, up to 30 minims. Boinet (1903), who used smaller doses—$\frac{1}{3}$ milligram of adrenalin—warns against large doses, and against treat-

ment in advanced cases. He also thinks the dose should be made smaller as treatment progresses, and the free intervals longer.

All these points should be carefully worked out experimentally, with as complete observation of patients as possible. As an example of the condition now, the blood pressure should be raised by specific glandular treatment. Many observers assert that it is, but some found no rise. That no effect is produced upon metabolism is only to be expected. It has been suggested that as the blood pressure raising action of digitalis resembles that of adrenalin, it could just as well be given. To a certain extent this is true, but, on the other hand, digitalis has no advantages over adrenalin in Addison's disease and is no freer from untoward effects. The danger of arterial degeneration under treatment must be borne in mind.

To sum up this part of the subject, the use of adrenal preparations in Addison's disease is legitimate, but they should not be given to the exclusion of symptomatic treatment. They are more promising in the early stages, and must be used with extreme care in advanced cases, but even in the latter are permissible. The preparations must be carefully selected as regards purity. The investigations of Reid Hunt[1] show that there is too much difference in the strength and quality of commercial preparations. No positive lines can be laid down for dosage and frequency of administration. The condition of the patient, and especially the blood pressure, muscular strength, and general sensations, should be carefully observed and used for the direction of further treatment. Busch and Wright report[2] a case of transplantation of a pig's medulla into the testis of a patient without definite effect.

The treatment in syphilitic cases must follow the known rules. In tuberculous cases, specific treatment with tuberculin preparations might seem indicated, but experience has shown that tuberculin in Addison's disease is very often followed by alarming symptoms. Perhaps the reaction in the vicinity of the affected tissue causes acute functional disturbances. While a cautious use of tuberculin in the hands of one who is accustomed to it, and with all proper care of the patient, is justifiable, it would doubtless be safer to depend upon the general treatment of tuberculosis, on lines now familiar to all. This can be considered with the symptomatic treatment, as the principles are precisely the same.

Symptomatic Treatment.—This is based upon the clinical features of the disease. For the muscular and cardiac weakness, rest is necessary, and should be more or less complete according to the condition. In the most severe stages the patient must not be allowed to raise his head or to exert himself in any way. Prolonged examinations may cause alarming or even fatal weakness. The body should be kept warm. The diet should at all times be nutritious and easily digestible. Eggs, milk, toast, soups, gruels, custards, cornstarch and arrow root, junket, buttermilk or fermented milk, or "milk foods" can be used. Meat is usually not craved or well borne. Dilute hydrochloric or tartaric acid may be given.

[1] *Arch. of Int. Med.*, 1910, v, 30.
[2] *Journal of the American Medical Association*, September 8, 1906, p. 790.

Gastric symptoms should be looked for, and upon the first indication of indigestion food should be stopped or reduced, according to the severity. If vomiting occurs or seems imminent the stomach should be carefully washed out with hot saline solution. Ice pills, carbonated water, or champagne may then be used, and if there is nausea, or tenderness, an ice-bag or a large mustard plaster may be applied to the epigastrium. Grawitz reports two cases "cured" by gastric lavage, and though one may doubt his explanation, the treatment must often be of decided value. Constipation should be guarded against by diet, mild enemas, or the mildest cathartics. Strong purgatives are never admissible, as they may cause fatal collapse. Diarrhœa should be treated by restriction of diet, enemata or colonic flushing carefully used, bismuth, paregoric, or other suitable opiates. Strychnine, arsenic, and other drugs have been used as tonics, and often seem useful. Digitalis may be given in small doses (5 minims of the tincture three times a day). An important aid in all cases is fresh air, due precaution being taken to prevent chilling. Bramwell has reported a case improved at a temperature near the freezing point, and patients may be out-of-doors in much colder weather without obvious harm, but for the outdoor treatment of such a disease very cold weather has serious drawbacks. For the heart weakness and syncope, that are so frequent, hot water bags should be applied over the heart, hot coffee given internally, or subcutaneous injections of strychnine, camphorated oil, or ether used.

CHAPTER XXI.

THE PITUITARY BODY. ACROMEGALY. HYPOPITUITARISM. POLYGLANDULAR SYNDROME. THE PINEAL BODY.

By GEORGE DOCK, M.D.

THE PITUITARY BODY.

The pituitary gland or hypophysis cerebri is a body of variable size, 6 to 10.5 mm. in sagittal, 10 to 14.5 mm. in vertical, and 5 to 9.75 mm. in transverse diameter (Zander), and weighing on the average, in health, 0.6 gram. It lies in the sella turcica or pituitary fossa of the sphenoid, attached to the base of the brain, behind the optic chiasm, by the infundibulum. Deposits of tissue representing epithelial accessory pituitary occur from the bottom of the sella to the vault of the pharynx.

It is composed of two lobes. The larger or anterior lobe is made up of follicles of various shapes, containing large "chromophile" cells with both "acidophile" (eosinophilous) and basophile ("cyanophile") granules, and smaller paler cells of indistinct outline, called "chief cells" (Stieda), "granule masses" (Rogowitsch), "granular protoplasm" (Schoenemann), or "chromophobe" cells. According to Benda, accepted by others, the various cells represent stages of a single class, the chromophile cells being more numerous in middle life, the chief cells in old age. Erdheim has shown the existence in the cells of fatty granules, which become larger and more numerous with age. In older subjects some of the follicles contain a material like thyroidal colloid, which also occurs between the follicles.

The posterior lobe is made up of connective tissue, bloodvessels, pigmented cells of various sizes and shapes, and also cells like those in the anterior lobe. Between the two lobes is the "pars intermedia," a partly vascular, partly glandular structure, with colloid in tubules and vesicles. The two lobes have separate blood supplies. The capillaries of the anterior lobe are "sinusoid."

The anterior lobe is derived from Rathke's pouch of the pharyngeal entoderm, the posterior lobe from the midbrain ectoderm.

Physiology.—Most of our knowledge is derived from operations for the removal of all or part of the pituitary body; feeding the glands, injections of their extracts, cytotoxic products and transplantation are all uncertain. Since Rogowitsch (1886) noted hypertrophy of the pituitary after removal of the thyroid, and Marie described acromegaly, very many have investigated the anatomy, physiology, and pathology of that organ. As the earlier literature is given in the admirable work of

Cushing,[1] and the newer articles fill considerable space in indexes, references will be avoided as much as possible in the following pages.

The pituitary body is probably essential to life; after its removal animals die in a few days or by two or three weeks, with severe cachectic symptoms. The secretion of the posterior lobe, which is poured into the cerebrospinal fluid, is related to metabolism, especially of carbohydrates, and to the growth of fat and other functions (Cushing). The anterior lobe has a secretion that is essential to life and to normal metabolism and development. Extracts of the gland contain a blood-pressure raising substance, acting by constriction of the bloodvessels; they depress the heart action; stimulate uterine and bladder contractions and contraction of the small intestine; increase diuresis; and have a galactogogue action. They increase protein metabolism and also that of calcium, magnesium, and phosphorus. Removal of the anterior lobe is followed by remarkable changes. Fat is deposited under the skin; the hair falls; there is polyuria, lessening of sexual activity, enlargement of the thyroid, and changes of bone growth and of temperament. The gland has a close relation to the sexual organs, shown in many ways. It becomes large and richer in eosinophile cells in pregnancy; becomes larger after castration; its extract stimulates growth of the reproductive glands and early and frequent breeding. It has well been called the growth gland par excellence, and is related to undergrowth as well as overgrowth. It also has a relation to sleep and hibernation.

The pituitary is intimately related in function to the other glands of internal secretion, but as Cushing says, its loss is felt more severely than that of any other. The topographic peculiarities of the gland should be borne in mind, as they probably have much to do with the contradictions in clinical and experimental observations. Like the adrenals, the pituitary body is a double organ, but the latter, lying in a closed space and subject to intracranial pressure, can hardly be affected in one part without affecting the functions of the other. Its relation to the optic chiasm and the base of the brain are of great importance in symptomatology and diagnosis.

Pathology.—Circulatory changes, from anemia to hemorrhage, are very frequent in the pituitary. Postmortem changes occur quickly, and have caused much confusion. Colloid and cystic degeneration are not rare; softening cysts, fibroid degeneration, and calcification are also not uncommon findings. Combinations of degeneration and hypertrophy of the gland are important, the latter giving rise to the adenoma or so-called struma of the pituitary. These may reach considerable size, cause pressure on the brain or optic chiasm, or erode the bones. According to C. Löwenstein,[2] they are frequent, especially in adults; are not characteristic of degenerated, but of developing organs, and should not be unexpected in cases of acromegaly.[3]

The numerous tumors described as sarcoma and carcinoma of the pituitary have in some instances been adenomata. Cases of undoubted

[1] Cushing. *The Pituitary Body and its Disorders*, 1912.
[2] *Virchows Archiv*, 1907, clxxxviii, 44.
[3] Swale Vincent, *Internal Secretions and Ductless Glands*, *Lancet*, 1906, ii, 348, 430.

sarcoma have been observed, as also carcinoma. In some cases of the latter, with metastases, defective development of the sexual organs has been observed. Acromegaly is not always present. Kollarits has collected 50 cases of tumor without acromegaly. Gummata, tubercles, and echinococcus have also been noted, and also without acromegaly. Teratomata and lipomata have been described. Secondary tumors are not rare; according to Simmonds they are limited to the pars nervosa or intermedia. Bacterial infections, especially with staphylococci and streptococci, occur.

The earlier literature shows hopeless contradictions between symptoms and anatomical change. There are still difficulties in many cases, but from the results of many careful observations, especially those of von Eiselsberg, Erdheim, Biedl, Lewis and Miller, Cushing, and others, we are now able to recognize some important forms of pituitary disease and to obtain a basis for further differentiation. Under the general head of dyspituitarism we can distinguish two types. One, recognized as acromegaly, was thought by many, even before the days of accurate experimentation to be due to hyperfunction, and though many steps are not known, the chief fact seems beyond doubt. Certain cases of giantism also probably belong here. Another condition, adiposo-genital dystrophy, has been more fully cleared up by experiment as a hypopituitary disease. A discussion of its symptoms offers a convenient place for the brief consideration of some other disorders whose relations to the pituitary body are not so well established. It must be remembered that among these conditions, which pass gradually into the normal constitution, or into bodily peculiarities that can hardly be called pathological, clinical pictures of the most varied and bizarre forms occur. It is, in fact, largely because of this fact that some of the most interesting, and by no means rare examples of disease have had to wait so long for recognition.

Therapeutics.—Various preparations of pituitary gland have been used. The most important are pituitrin, an extract of the posterior lobe, which contains the intermedia; pituglandol, from the infundibulum; vaporole, also from the posterior and intermedia. The anterior lobe has been experimented with a good deal clinically, but no definite statement of its action can be given.

ACROMEGALY.

Synonyms.—Acromegalia; acromégalie (Fr.); Akromegalie (Germ.); Pachyacrie (von Recklinghausen); Marie's disease.

Definition.—Acromegaly is a chronic disease characterized by an abnormal increase of the size of the extremities and of some internal organs, with cachexia, associated with morbid function of the pituitary gland.

History.—Knowledge of the disease began in 1886, when Pierre Marie described two cases of his own and others in the literature, and distinguished it from other diseases with some of the same symptoms. This led to a new study of giantism, in which von Langer made a beginning in 1872. Von Langer had described two types of giant crania, one normal, large but well formed, the other with a larger sella turcica and

enormous lower jaw, with other features now well known as acromegaly. He also pointed out the enlargement of the soft parts, and from the alteration of the sella turcica concluded there had been degeneration of the pituitary body.[1]

It is not necessary in a work of this kind to speak in detail of giants, although they belong more to medicine than to anthropology. The current idea of a giant is probably that of Geoffroy St. Hilaire—"an individual superior in size to that of the race," but this is too general. Meige (1902) made a useful classification into normal and pathological giants, the former rare, the latter less so, which agrees in general with the division of von Langer, but is more accurate in detail. Anthropologists make an arbitrary classification, those above 2 meters (6 ft. 8 in.) in height being termed giants. Clinically it is more accurate to make a further classification, and we can, with Roy, speak of transitory or precocious giants, such as occur sometimes at puberty, infantile giants, resembling eunuchs and castrated animals in many particulars, and acromegalic giants. The giantism may be partial, affecting any part of the body. Sometimes the fat is hypertrophied. It is not always easy to distinguish accurately the various classes. Some individuals looked upon as true giants have proved to be acromegalic. So far from being superior creatures as is often thought, even the most "normal" giants are physically and functionally defective in many ways. They are relatively and sometimes absolutely weak; they often have large or deformed extremities, even if not clearly acromegalic; they are all mentally inferior, furnishing "more drum-majors than Academicians"—and all die young, usually between twenty and thirty.[2]

Etiology.—Acromegaly is a comparatively rare disease, but has been found in all parts of the world, among all races. Berkeley described the first negro case, Dana that of an American Indian. The two sexes are are about equally disposed to the disease.

Acromegaly occurs most frequently in the third decade of life, very rarely in the second or after the fourth, although in women it seems to begin, on the average, later than in men. Moncorvo's case in a child aged fourteen months, is considered not acromegalic, probably cretinous. It affects especially people of large size. According to Sternberg 20 per cent. of acromegalics are above six feet in height when symptoms begin, while 40 per cent. of giants are acromegalic. Dwarfs, however, are not immune. A family predisposition has been noted; also diabetes in the ascendants and goitre in the patient or immediate relatives. Among the causes assigned we find inherited nervous disease, alcohol, lead, syphilis, emotional shock, such as fright, various infectious diseases, typhoid and scarlet fever, poisoning by illuminating gas, and trauma. Very often the history or an old photograph will show that the disease

[1] Besides the work of Souza-Leite inspired by Marie, those of Collins (1892), M. Sternberg (1894, 1897), Brooks (1898), and O. T. Osborne (1892, 1897, 1899, the *Reference Handbook of the Medical Sciences*, 1900, vol. i), and Cushing should be consulted, while the "*Acromegaly, a personal experience*" of Leonard Mark, London, 1912, has a peculiar interest. Interesting references to early literature are given in the study of Felix Patry, *L'Acromegalie avant* 1885, Paris, 1908.

[2] See Launois et Roy, *Étude biologique sur les Géants*, 1904.

antedates the alleged cause, although the latter may sometimes hasten the progress of the disease.

Pathology.—It was supposed at first that acromegaly was due to lack or suppression of the internal secretion of the pituitary, but more recent histological and experimental work indicates that hyperfunction is more probable, and that altered functions of other ductless glands, including the internal secretion of the sexual glands, have important but as yet obscure relations to the disorder of nutrition that causes so many of the striking features of the disease. Keith, showing the resemblance of acromegalic skulls to those of anthropoid apes and to paleolithic skulls, suggests that the pituitary hormone sensitises the tissue, and that mechanical stimuli cause the growth. (*Lancet*, 1911, Apr. 15.)

Morbid Anatomy.—*Bones.*—Although the enlargement of the extremities is usually the most striking anatomical alteration, all the bones of the body are more or less affected. As in the extremities, however, the process is not a general enlargement, but an exaggeration of bony prominences, crests, ridges, tuberosities, etc. The grooves for tendons, vessels, and nerves are often of unusual depth. The process is due to periosteal growth, and osteophytes are common. The bones are often increased in density in the outer parts, but the spongy portion is often lighter than normal. Hans Curschmann calls attention to degenerative processes, causing atrophy of the bones of the hands and feet. He found this in three cachectic cases. Among the individual bones some show alterations that deserve particular mention.

The cranium is often deformed by osteophytes and a great exaggeration of the occipital, mastoid, and other prominences. The orbital arch is large, the frontal prominences conspicuous, the zygoma, malar, and nasal processes all increased in size. The glenoid fossæ are larger and wider apart than normal. The lower jaw is almost always enlarged in all directions. The cranium is usually irregularly thickened, and is remarkable in most cases for the enlargement of the sella turcica. The sphenoidal sinuses are large, the antra of Highmore also, as are all the accessory sinuses. The vertebral column is always deformed in advanced cases, with kyphosis of the cervical and upper dorsal regions. The vertebral bodies are not altered, except secondarily, but the processes and borders are enlarged.

The most striking alteration is usually in the extremities, viz., enlargement of the hands and feet, but with the exception of the terminal phalanges, which are often broad and thick, with exostoses in variable size and number, the bones of the extremities are rarely really enlarged. If they are, the process is not considered essential to acromegaly.

Skin and Subcutaneous Tissue.—Examinations postmortem show that the enlargement of the extremities is not chiefly bony. X-ray examinations show the same thing, as described by Schultze, Schlesinger, Edel, and others. It is therefore more accurately described as pachyacria than acromegaly. The subcutaneous tissue is thickened by connective tissue growing in and around the fat lobules, sometimes forming fibrous tumors. Similar growths surround the sweat glands and nerves, or sometimes pass between the nerve fibres. The hair follicles, sweat glands, and

bloodvessels in the skin are not notably altered. The connective-tissue overgrowth also occurs in the muscles.

The *pituitary gland* is often enlarged, as it was in the early case of Verga (1869) and in von Langer's pathological giants. Sometimes the gland is described as normal, but obviously enlarged beyond the average. Sometimes the enlargement is only moderate, up to the size of a cherry, but with erosion of bones, indicating abnormality. It may reach the size of an apple, growing down to the pharynx, or up into the base of the brain, and outward into the lateral sinuses. The anterior lobe is especially involved. Of the alterations described, the most frequent are: hyperplasia or adenoma, cystic, fibrous, "malignant" adenoma, sarcoma. Hanau showed that the so-called sarcomata are derived from the epithelium of the gland, so they are better named malignant adenomas. Benda's theory of pathogenesis is now generally accepted. He thinks the hyperplasia of functionating cells is present in all cases of acromegaly, but that in the further course of the disease either a malignant degeneration of the hyperplastic tissue, or some other tissue, replaces the functional cells.

The other ductless glands show no constant change. If altered, the condition is not always easy to distinguish from a complication. The adrenals are larger, normal, or slightly atrophied. The thyroid gland is almost always abnormal, being either large and goitrous or atrophied. In a case in the writer's clinic, Warthin found the parathyroids hyperplastic, weighing 1.5 to 1.7 g., with cystic dilatation of the lymph spaces. The thymus is often enlarged. Benda found the carotid glands small, but normal. The pineal gland has been found enlarged. The dura and pia arachnoid are sometimes calcified or even contain bony plates not, of course, peculiar to acromegaly. The brain is sometimes described as large. The most important changes are those due to pressure, especially in the region of the infundibulum, chiasm, and pons. Various degenerative changes have been found in the spinal cord. The peripheral nerves are sometimes affected as already described. Barrett has reported an interesting case. Degeneration of the cervical sympathetic has been described in some cases. In many others it was normal.

Enlargement of internal organs, or "splanchnomegaly," has been described, involving especially the kidneys, liver, heart, and spleen. In one of Osborne's cases the heart weighed forty-one ounces. The pericardium is sometimes thickened.

While the external genitals are usually hypertrophied, the uterus, ovaries, and testes are often hypoplastic or degenerated.

The pancreas is sometimes the seat of connective-tissue overgrowth.

Symptoms.—The acromegalic patient is usually able to give a history of important symptoms long before the characteristic deformities occur. Headache, frontal or vertical and often excruciating, irritable temper, moroseness, pains in various other parts of the body, including the joints, disturbances of vision, loss of memory, tingling or numbness of the extremities, increased appetite and thirst, constipation, polyuria, and various dyspeptic symptoms, are the most frequent early phenomena. In women amenorrhœa is frequently but not always noted; in men, sometimes, loss of sexual power. Variations in the course of the symptoms

can often be discovered, and sometimes a gain in weight. If besides some of the symptoms noted there is a statement of increased growth, either general or in the "ends" of the body, suspicion should at once be entertained that the case is one of acromegaly. A comparison of old photographs will often assist in showing the changes of the extremities, but as Benda has pointed out, care must be taken to avoid mistake by the perspective errors common in photographs. Changes in the sizes of hats, gloves, and shoes are more trustworthy. The latter may increase two or three sizes. Sometimes the abnormal growth begins before the subjective symptoms, but is not considered a sign of illness.

FIG. 62

Acromegaly. Original observation. The size of gloves changed from $6\frac{1}{4}$ to $8\frac{1}{2}$, and of shoes from 3 to $5\frac{1}{2}$.

The head shows unusually arched and prominent brows, with the forehead retreating. In one of the writer's adult cases the hat-size changed from $6\frac{7}{8}$ to $7\frac{7}{8}$. The skin of the forehead is wrinkled. The nose is large, sometimes enormous. The nasal mucosa is often thickened. Epistaxis is a frequent symptom. The zygomas and malar prominences are exaggerated. The upper jaw is seldom notably altered, although the antra of Highmore are enlarged. The upper lip is often long and thick. The lower jaw is almost always enlarged, although in some otherwise typical cases (Gauthier, Campbell, Whyte) it has not been so. The bone is enlarged in all directions, so that the condyles are farther apart than normal, the rami longer and wider than normal, the symphysis thicker and uneven. The lower teeth may be 2 cm. or more beyond the upper

ones. The alveolar process is, as it were, rolled out, the teeth farther apart than normal, "enlarged" in one case. The face is generally oval ("type ovoide" of Marie), often spoken of as prognathous, but not strictly so, and more accurately spoken of as progenic ("cranium progeneum"). When the jaw is not prominent the face is spoken of as square ("type carrée" of Marie). The chin is thick. The head tends more and more to lean forward, and the chin may come to rest upon the sternum.

The eyes may be found of normal size and position in the large orbital cavities, or there may be exophthalmos from bony growths or increase of soft parts in the orbit, or even actual enlargement of the bulbs. The lower eyelids are often thick. The ridges in the occipital region are usually much increased in size. The tongue is almost always large, although Dreschfeld saw a case with large lower jaw and tongue of normal size. It may be so large as to force the mouth open, and it plays a part in the deformity of the alveolar processes. The tongue is usually indented at the sides, fissured, and the papillæ enlarged. The soft palate and uvula are often thickened.

The larynx is sometimes large and its mucosa thickened generally or in various parts. Corresponding to the changes in the mouth and larynx, the voice is often affected, deeper in pitch than before, and speech is slow and thick. The submaxillary, salivary, and cervical lymphatic glands are often enlarged.

Kyphosis, kyphoscoliosis, and lordosis are present in various degrees, sometimes observed early, usually increasing in the advance of the disease, and causing a marked decrease in height. The thorax is often large, especially in the anteroposterior diameter, the ribs are often thickened at the ends, their motions interfered with, and respiration largely abdominal as a result. The sternum is enlarged, thick, and uneven. The spinous processes of the vertebræ are often much enlarged. The clavicles are generally thick and sometimes enlarged in all directions. In comparison with the size of the thorax the abdomen often looks small, and is rarely pendulous. The pelvis is often enlarged by bony growths on the crests and tuberosities of the bones. The sexual glands early lose their function. Conception is very rare.

The shoulder-joints are sometimes large, also the elbows, but the forearms are often thin and weak, and look still smaller on account of the increased size of the hands. The latter occurs under two different forms. In one the hand is long ("type en long," or giant type of Marie), more frequently broad ("type en large," or massive) and paw-like. The fingers in this type are thick, sometimes clubbed at the ends, sometimes "sausage-shaped." The skin of the hands is thick, the subcutaneous tissue also. The nails are often short, thick, brittle, and striated. Although the bones of the hands and fingers are sometimes increased in length, most of the enlargement comes from the increase of the subcutaneous tissue, with exostoses and increase of the points of attachment of the tendons.

The knee-joints are sometimes enlarged, also the patellæ. Crepitus may be present in the joint. The ankles and feet show a more decided enlargement. The enlargement of the os calcis backward, and of the great

toe, and an enlargement of the outer side of the foot cause a very characteristic feature of the disease. The skin and soft parts of the feet show alterations like those of the hands. The subcutaneous tissue in general is often thickened by connective-tissue overgrowth. Later this is followed by atrophy. The skin in general is often yellowish or brown. Over the nose it is sometimes red, with enlargement of the sweat and sebaceous ducts. The skin is usually dry, but perspiration is easily provoked. The hair usually grows well and it may be increased on the body. Nævi, mollusca fibrosa, fibromas, sometimes painful, and lipomas often occur in the skin. Flushing, tingling, sweating, and other vasomotor changes in the skin are frequent. Hemorrhoids and varicose veins are not rare. Verstraeten observed high fever, but, as a rule, the temperature shows no marked alteration.

The muscles show no marked change in the early stages or may be increased in size and strength. Later they become small and weak, a change that has much to do with the peculiar way of holding the head, and the kyphoscoliosis and other deformities. Great weakness may occur temporarily in various muscles.

The pulse is rarely accelerated. The heart usually becomes hypertrophied. Later, dilatation and loss of compensation, with great œdema, become important factors in the case. Sclerotic changes in the blood-vessels are often present. Dyspnœa is frequent, from weak heart or from the changes in the bony thorax.

The stomach is sometimes large, probably due to polyphagia. The liver and spleen are often palpably enlarged.

Many of the nervous symptoms in the disease are directly due to the pituitary tumor so often present. Uhthoff[1] has explained why pressure symptoms are not still more frequent. Ward Holden (1900) has described the mode of involvement of the optic chiasm. The diaphragm of the sella turcica prevents enlargement forward for a time. Affections of the oculomotor nerves occur when the tumor grows backward; if it increases sideways the abducens becomes affected. Affections of the sight occur in more than half the cases. Blurring of vision, concentric narrowing of the visual fields, bitemporal hemianopsia, and optic atrophy with amblyopia to amaurosis are encountered. The pupils are generally normal, but may be dilated. Nystagmus and strabismus occur. The retina is often congested. In some cases only one eye is affected.

The external ears are often large and thick. Deafness is not infrequent, and from pressure on the cavernous sinuses, tinnitus aurium is frequent and often painful, especially on lying down. The external auditory canal is sometimes enlarged, the membrana tympani thickened. Smell and taste are rarely affected. Paresthesia of the extremities is a frequent symptom. The tactile sense is sometimes lessened in the hands and feet. The reflexes are not notably affected in most cases. Beduschi has reported a case in which the knee and Achilles reflexes were absent, and with amyotrophic palsy and alterations of faradic excitability.

Loss of memory, slowness of mental processes, and depression or delu-

[1] *Berl. klin. Woch.*, 1898, Nos. 22, 21, 25.

sions are frequent. Bursts of anger are likely to occur, or insanity with suicidal or homicidal tendencies. Epilepsy is sometimes combined with acromegaly as described by Farnarier and also Shanahan. Somnolence is often a marked symptom, and may pass into stupor. Vertigo and syncope are not unusual. Part of the nervous symptoms are due to pressure, but others depend upon more indirect causes, toxic, circulatory, or pain, weakness, or the exhaustion from complicating diseases like diabetes, nephritis, or myocarditis.

The blood becomes affected in the later stages, showing low coloring matter, diminished red cells, slight leukocytosis, and a relative or absolute increase of mononuclear and eosinophile cells. Franchini observed lipemia even in non-diabetic cases, and an excess of calcium and magnesium. Hemoglobinuria has been observed by Chvostek, who looks upon it as the result of a vasomotor anomaly due to pituitary disease.

The urine shows no characteristic change. A very frequent occurrence is glycosuria, the cause of which is still unsettled. Benda found it without alteration of the pancreas. That it is cerebral and due to the pituitary disease seems borne out by the fact that diabetes is most marked with the largest tumors. Borchardt,[1] in reports of 176 cases of acromegaly, found diabetes noted in 63, and alimentary glycosuria in 8 more, indicating a lack of carbohydrate metabolism in 40.32 per cent. of all cases. Anders has recently analyzed the cases since Borchardt's report. Out of 183 cases of pituitary disease with urinary findings, 88 had acromegaly, and 16 of these had glycosuria, with two more doubtful. Albuminuria with casts occurs as part of a complicating nephritis in many cases.

The metabolism of acromegaly is not characterized by constant changes in any respect, judging from the few reports in the literature. Bulimia, diabetes, Basedow's disease, and myxœdema cause modifications, as might be expected, when they occur with the disease. Edsall and Miller[2] concluded there was retention of phosphates in the bones and muscles, and increase of urinary calcium. They point out that the metabolism suggests metabolic abnormalities rather than mere overgrowths, so that further researches in the same field are urgently indicated. Feeding with large quantities of pituitary tablets also has little effect, either in health or in acromegaly (Salmon, Magnus-Levy, Schiff, Franchini).

The *course* of acromegaly is very variable. The early subjective symptoms are usually long misunderstood. The remissions of the disease add to the confusion, so that a sudden increase of symptoms following some acute illness or an accident first calls attention to the nature of the process. The remissions may last many months or even years. The duration is obviously difficult to estimate. The usual classification as regards duration includes three forms: Benign, with mild symptoms and a duration up to fifty years; chronic, lasting from eight to thirty years; acute or malignant, ending in six years. The majority of cases belong to the chronic form. Sternberg has called attention to malignant cases, with enlargement so rapid that it can be seen by the physician. In all the cases observed there was malignant disease of the hypophysis. Other

[1] *Zeits. f. klin. Med.*, 1908, lvi, 332.
[2] *University of Pennsylvania Medical Bulletin*, March, 1903, p. 143.

varieties are based upon individual clinical features. Duchesneau has called attention to an amyotrophic, Sainton to a neuralgic, and Beduschi to a paralytic form. The terms "pseudo" and "fruste" have been applied to cases with very atypical features. Marek has reported transitory acromegaly in pregnancy.

Acromegaly is often combined with some or many symptoms of other diseases, especially exophthalmic goitre, syringomyelia, myxœdema, and epilepsy. Horsley,[1] in fact, looks upon epilepsy as one of the common features of pituitary tumor.

Diagnosis.—The diagnosis in a typical case is very easy. In the early stages it may be difficult, and it is also difficult to exclude from acromegaly certain examples of various diseases that in some respects resemble it, especially all those associated with local enlargements of the extremities. Brain tumor, arthritis deformans, Graves' disease, diabetes, and progressive muscular atrophy have been supposed to be present alone in many cases, although the whole history and physical condition, if carefully investigated, would quickly reveal the true state of affairs. Acroparesthesia, especially at the time of climacteric, has been supposed to be present, and until enlargement of the "ends" reveals the true condition the mistake might be difficult to avoid.

It is essential to realize that enlargement of a single extremity or of all the extremities is never enough for a diagnosis. The enlargement of the other ends of the body is much more important, and there must also be some of the nervous, eye, or subjective symptoms. The recognition of a brain tumor in any case, with a localization at the base of the brain and near the chiasm, would lead one to look for disorders of growth, so that the differential diagnosis of the former need only be referred to here. It is important to consider some of the diseases that from deformity may be wrongly classed with acromegaly. Myxœdema has frequently been so mistaken. The skin and the mental condition are often much alike in the two diseases. The absence of bony enlargement, the thick myxœdematous pads, the loss of hair, and low temperature are important signs. Cases of myxœdema combined with acromegaly require careful weighing of all the signs, as well as investigation of the less obvious features of both diseases. The confusion with cretinism can hardly stand a careful investigation of the early history.

Erythromelalgia has been mistaken for acromegaly, but a careful examination would prevent error, by disclosing the marked vasomotor feature of the former, and the absence of the characteristic features of Marie's disease.

Giantism is to be differentiated by the absence of acromegalic characteristics. These should be looked for in all giants, especially when changes of figure or other signs of illness occur. Giants with unsymmetrical lesions of bone, from local disease or syphilis, must be distinguished by attention to the general rules.

Osteitis deformans (Paget) differs from acromegaly in the absence of enlargement of the soft parts, the tendency to curving of the tibiæ and

[1] *British Medical Journal*, 1906, i, 323.

other long bones, the more advanced age of onset, the greater tendency to unsymmetrical enlargement, and the absence of the enlarged lower jaw.

Arthritis deformans is sometimes associated with great enlargement of the feet, less frequently the hands, although the great size and thick fingers and toes of acromegaly are not usual in the former. Kyphosis is sometimes present. The two diseases may be combined, in which case, as in others of difficulty, the course of the disease, the subjective symptoms and the condition of the soft parts would be of great importance.

Pulmonary osteo-arthropathy is to be differentiated by the presence of or history of bronchitis, emphysema, or other diseases of the respiratory tract, the absence of enlargement of the soft parts of the hands and feet, and the curved nails at the clubbed ends of the fingers and toes.

Hyperostosis may cause serious difficulty in diagnosis, either in leontiasis ossea, affecting the cranium alone, or in the diffuse form. The disease usually begins in early life, may cause deformities of the vertebral column, with exophthalmos, blindness, deafness, imbecility, and death. It may be combined with acromegaly. Cases of this kind cannot be understood until the whole subject of growth is cleared up.

The clinical diagnosis of the various partial overgrowths of fingers, toes, etc., cannot often be made without an accurate idea of the nature of the morbid process, which may prove to be related to acromegaly. All these cases need to be investigated with reference to the pituitary and other ductless glands.

Adiposis dolorosa, multiple enchondroma, elephantiasis, lymphangitis, scleroderma, and trophœdema have at times caused difficulty in diagnosis. Thorough examination alone can prevent serious errors.

The value of skiagraphic examination of the bones of the extremities and of the skull must be remembered, and use made of it for diagnosis.

Prognosis.—This varies with the determination of the variety, the presence or absence of complications on the part of vital organs, and the possibility of giving the patient all the care a disease so rich in symptoms requires. Œdema of the brain, uremia, severe heart weakness, and severe diabetes are the most serious signs. Cases in which an early operation on the pituitary can be successfully performed may enable the prognosis to be modified, but it is too early to foretell the ultimate result in such cases.

Treatment.—Efforts to treat acromegaly with extracts of the pituitary and thyroid have been made by many, but, on the whole, with disappointing results. At the same time, further experiments with organic preparations are legitimate, and the progress of discovery in the physiology and pharmacology not only of pituitary extracts, but of those of other organs, should be carefully followed in order to learn indications of value. Thyroid extract may be useful in cases with myxœdema symptoms, and should be used, with proper care, in such cases. While many have had bad results from pituitary extract, Osborne's experience is interesting and encouraging. Giving from six to twelve grains a day, he saw improvement of many symptoms and of the hypertrophies.

In case a pituitary tumor can be recognized, an effort should be made to treat it surgically, especially if the pressure symptoms are severe.

Schloffer, Mozkowicz, von Eiselsberg, Hochenegg, Cushing and others have shown how much can be accomplished in certain cases. By some the nasal route has been preferred to the frontal, sometimes assisted by *x*-rays. Not only improvement of tumor symptoms, but also diminution of the enlarged parts and of the subjective symptoms, have been obtained. Horsley has pointed out that in such cases "the first duty of the surgeon is to relieve mechanical pressure; to do it so as to avert blindness, and to prevent a fatal result."

The symptomatic treatment must be directed to the relief of symptoms and complications. Analgesics and sedatives will often be required for painful conditions. Diet can often be arranged so as to improve constipation or glycosuria. Potassium iodide, mercury, and arsenic have been thought of benefit. Cardiac weakness, nephritis, and symptoms associated with them must be treated as under other circumstances.

HYPOPITUITARISM.

Synonyms.—Pituitary dystrophy; Typus Fröhlich; Fröhlich's Syndrome; Degeneratio *seu* dystrophia adiposo-genitalis (Bartel); Syndrome hypophysaire adiposogénital (Launois and Cleret).

The relation of pituitary disease to adiposity, suspected long before, became probable when Fröhlich (1901) asserted the pituitary origin of adiposity with genital infantilism, and was assured by the study of a large number of cases, in some of which operations were performed on the hypophysis, and especially by the experimental work of Aschner, Ascoli, Biedl, Cushing and his associates, and many others. Much has still to be done in order to clear up seeming contradictions and fill out details in etiology and pathology.

Typus Fröhlich.—The most striking and characteristic example of hypopituitarism, as we see it in disease of that organ or in experiments on animals, shows general or local fat accumulations tending to produce feminine outlines or those seen in certain eunuchs, arrest of development or atrophy of the sexual apparatus with corresponding changes of the primary and secondary sexual characteristics, delayed skeletal growth and ossification, lowered metabolism, polyuria, and symptoms of pressure on the optic nerves.

Symptoms.—One of the chief symptoms is the excess of fatty tissue, in varying degrees, all over the body, but especially on the hips, nates, mons veneris, mammæ, abdominal wall, supraclavicular regions or neck, or extremities. In some cases it is absent or is very slight, and only discovered by careful examination, bearing in mind the normal distribution of fat in the male and female, respectively.

The skin is usually pale, has been compared to alabaster, is cool and dry, sometimes scaly. Perspiration is absent or diminished. As in myxœdema, the appearance of the skin sometimes leads to a diagnosis of chronic nephritis.

Bones.—The bones show various kinds of changes, including dwarfism on one hand and eunuchoid giantism on the other. When the disease occurs early the growth and fat are most obviously affected; when it

occurs later, the fat and genital dystrophy. The resemblance of hypopituitary cases to castrated animals has led to the supposition that in Fröhlich's type the primary disease is in the interstitial tissue (cells of Leydig) of the sexual glands. But genital atrophy is not always present, especially in the beginning. Falta shows that the peculiarities of bone growth depend on the preponderance of one of two factors—the genital, causing the eunuchoid type, the hypophysis, the infantile. He also points out a difference in ossification. "In mild degrees of pituitary disease ossification is but slightly affected; in severe cases centres of ossification and epiphyses are both affected, whereas in eunuchoidism failure of epiphyseal closure is paramount, and remains so a long time."

The changes in the genital sphere are essential to the recognition of the disease, and to all dystrophies involving the bones and adipose tissue. In males the penis and scrotum are infantile in size and shape, the testes minute, sometimes undescended; the prostate small. In woman the external genitals, ovaries and uterus are infantile. The internal sexual organs are often impossible to examine fully on account of obesity. The mammæ may be large but lack glandular tissue. The growth of hair is infantile. In men the beard does not grow; the crines pubis and axillæ are absent, or there is scanty pubic hair with the feminine distribution. The unusual growth of hair seen in some cases in women probably indicates polyglandular disease. The voice does not change in boys. There is no libido or ejaculation. Menstruation is irregular or absent. In cases developing after puberty, sexual characteristics are lost.

The details of metabolism have not been completely investigated as yet, but high carbohydrate tolerance is usually present. Many patients cannot take enough glucose to give reduction in the urine, amounts up to 500 grams being assimilated. Cushing found the blood sugar low.

Polyuria is a frequent symptom, and there is sometimes severe and typical diabetes insipidus. Frank ascribes so-called idiopathic diabetes insipidus to hyperactivity of the pars intermedia.

The low body temperature responds to injections of pituitary body extract. Cushing was able to cause elevation of temperature in cases of hypopituitarism by injections of 2 cc. of a 5 per cent. solution, and Falta and Kahn confirmed this and found no reaction in other conditions.

The blood shows reduction in the number of red cells; the hemoglobin is proportionately lower; there is leukopenia with mononuclear cells, lymphocytes, and eosinophiles increased.

"Neighborhood symptoms," due to tumor, are not always obvious, and the sella and the mental and nervous symptoms should be carefully examined in all suspicious cases. A negative finding in the Röntgenogram does not permit the exclusion of pituitary disease, especially one with lowered function. Evidences of disease of the middle cerebral region must be looked for—headache, eye symptoms with special reference to hemianopsia, amblyopia, amaurosis, atrophy, and choked disc. In hemianopsia the fields for colors may show changes before the white. Other cerebral symptoms often present are vertigo, vomiting, somnolence, epilepsy, and disorders of taste and smell.

Exophthalmos has been noted rather frequently, and has been explained by pressure from tumor, by fat in the orbits, paralysis of muscles, hyperthyroidism, and adrenal influence.

Besides sweating, other vasomotor phenomena have been observed, especially dermographism.

Symptoms on the part of the naso-pharynx are not rare, and include suppuration, polyp, and escape of cerebro-spinal fluid.

Pathological Anatomy.—Kollarits and von Frankl-Hochwart have collected many of the recorded cases. The changes vary even more than they do in acromegaly. Various kinds of tumors, secondary as well as primary, occur, also cysts, and numerous lesions of the neighboring organs causing pressure on or destruction of the pituitary. The latter include dural endothelioma, cholesteatoma, aneurism, syphilis, tuberculosis, and echinococcus. Madelung reported a case of gun-shot wound with the bullet in the sella. Various lesions causing pressure on the infundibulum, including chronic hydrocephalus, have been noted. It should be remembered that brain tumors outside of the pituitary region have been associated with adiposo-genital dystrophy, so that failure to discharge secretions has been suggested. Cushing points out that hypofunction of both lobes seems probable.

The thyroid gland is often abnormal, in various ways; the thymus is frequently large, and this is sometimes associated with other signs of lymphatic disposition; the adrenals and pancreas are also in some cases hyperplastic. Disease of the pineal gland may be associated.

Varieties and Allied Conditions.—In some cases a combination of acromegaly and adiposo-genital dystrophy occurs. This may represent secondary lowered activity of a previously hyperactive gland, or there may be hyperplasia of the anterior lobe with increased function, checking the secretion of the posterior lobe.

Many experimental and clinical findings have led to the supposition that many or even all forms of adiposity, including Dercum's disease, are of hypophyseal origin. The extensive article of Lyon[1] gives a useful resumé of the most important recorded cases, and many original ones.

Experiments and analogy suggest the close relation of various kinds of dwarfism and pituitary disease. Many have looked for this explanation in achondroplasia, so far without satisfactory results.

If some cases of that interesting variety of dwarfism called *ateleiosis*, the pituitary has been diseased. In this condition the subject is born a dwarf and remains of childish stature and ossification, but with the parts of the body in due proportion (except the nose, which is striking in its size and aquilinity). This condition contrasts strongly with that named *progeria* by Gilford, in which with arrest of growth there is premature senility.[2] Keith suggests that ateleiosis stands in the same relation to progeria that giantism does to acromegaly.

Differential Diagnosis.—Adiposity and infantilism require in all cases careful investigation into the underlying causes. The many causes of

[1] *Archives of Internal Medicine*, 1910, vi, 28.

[2] See the valuable work of Hastings Gilford, *The Disorders of Post-Natal Growth and Development*, London, 1911.

infantilism need not be mentioned here. Eunuchism and eunuchoidism call especially for examination of the sella, but it must be borne in mind that in some cases of hypopituitarism there may be no neighborhood symptoms and no Röntgenologic abnormality. The latter is true of gumma, tuberculosis, and atrophy. A knowledge of the sexual characteristics is essential, and the work of Tandler and Grosz[1] will be helpful in that respect. Disease of the pineal gland and the thyroid must be considered.

Prognosis.—The course of hypopituitary disease varies extremely, depending chiefly on the question of malignancy and the direction of pressure of tumors or cysts. In many cases there are remissions, which sometimes lead to almost complete restoration of eye functions, and disappearance of cerebral symptoms. Improvement has followed the rupture of a cyst from a blow on the temple, or from destruction of the sphenoid. In non-malignant cases the duration may be very long. At any time increased intra-cranial pressure, epilepsy, or accidental complications may hasten the end.

Treatment.—Much depends on the chances of operation, not only for the prevention of loss of vision, but for removal of the functional disease. It is urgently indicated in cases with dangerous pressure symptoms. In other cases the risk of removing healthy tissue must be remembered. Experimental operations would seem worth making in any case, but patients often refuse to avail themselves of the opportunity.

Trials with pituitary extracts are also worth making, and should be used as far as possible, especially in cases where accurate observations on symptoms and metabolism can be made. In the hands of Cushing and others promising results have been obtained. For the adiposity thyroid preparations have been used, but with indifferent results. Puncture of the corpus callosum (Anton), and *x*-rays have been used for relief of pressure, and deserve further application.

POLYGLANDULAR SYNDROME.

The early suggestion of Pineles (1899), that probably in all cases of ductless gland disease several, in some cases all, the endocrinous glands are altered in function if not in structure, has been abundantly confirmed. Recently, there has been a tendency to speak of polyglandular disease, even in cases in which the useful rule "a potiori fit denominatio" might give a simpler name. The French especially, owing to the facility their language offers adjectives, have erected a series of such diseases or syndromes. The time may come when they can be accurately applied, but at present they foster unfounded diagnoses. There is one group in which the obscure sclerosis of the adrenals participates, and in which the thyroid, sexual glands, and pituitary body are also affected. To this group we may, with Falta, apply the term with some advantage. The symptoms combine those of myxœdema, late eunuchism, adiposity, and other pituitary anomalies, and pigmentation and other signs of Addison's

[1] Tandler and Grosz, *Die biologischen Grundlagen der sekundaeren Geschlechtscharaktere*, Berlin, 1913.

disease. A number of cases have been recorded, and as the anatomical examinations of ductless gland disease are more accurately made it is probable the proportion will increase. They emphasize the necessity of tracing out all the relations in all cases of ductless gland disease.

It is possible there is a converse to the syndrome, one with symptoms of hyperfunction of the gland named and possibly others, but it is more difficult to distinguish.

THE PINEAL BODY.

The pineal body lies under the posterior end of the corpus callosum, covered by the pia mater, having arisen from a diverticulum of the third ventricle. It measures about one centimeter in length, one-half centimeter in width, and weighs about 0.2 gram. Its interesting embryology need not be detailed here. It is made up of acini in a fibrous capsule, and contains cells with eosinophile granules, also basophile, albuminous, and lipoid granules, glia and ganglion cells. Involution begins about the seventh year, and is associated with the formation of "brain sand," but some of the glandular tissue persists up to advanced age.

Physiology.—Long looked upon as a vestigial remnant, the pineal body was shown to have important functions by investigations of Howell (1898), von Cyon, Halliburton and Dixon, Ott and Scott, Eyster and Jordan, and others.[1] It is certain the body has a close relation to growth, sexual development, and metabolism.

Pathology.—Some of the most important facts are derived from cases in which the gland was more or less destroyed by disease. It is not infrequently affected by various degenerations, infections, and tumor formations,[2] teratoma being especially frequent. In castrated animals the body is sometimes found atrophied.

Symptoms.—The symptoms of pineal disease—hypo- or dyspinealism (Marburg), apinealism (Foà)—are partly local, partly trophic. The former may be understood from the topography of the body, and belong to the study of brain tumors.[3] The trophic changes, more marked in young subjects, include increased growth, psychic and physical precocity, with unusual size and early function of the sexual organs, growth of beard and body hair in boys especially, and change of voice, and adiposity, to which cachexia is sooner or later added. The diagnosis cannot be made with certainty, but should be attempted on the basis of the facts known, and with reference to other diseases of the ductless glands.

[1] See the valuable report of Dana and Berkeley, *Medical Record*, May 10, 1913.
[2] Goldzieher, *Virchows Arch.*, 1913, ccxiii, 353.
[3] See the excellent study of Bailey and Jelliffe, *Arch. Int. Med.*, 1911, viii, 851.

CHAPTER XXII.

DISEASES OF THE THYROID GLAND.

By GEORGE DOCK, M.D.

ANATOMY AND PHYSIOLOGY OF THE THYROID.

The thyroid is a ductless gland composed of two lobes lying on each side of the larynx, and joined in most cases (80 to 85 per cent.) by a middle lobe or "isthmus" which crosses at the third and fourth rings of the trachea. The isthmus may be free from the lateral lobes. When it is absent, the lateral lobes lie close together. In front the thyroid is covered by the sternohyoid, sternothyroid, and omohyoid muscles. At the sides it reaches or overlaps the sternocleidomastoid muscle and partly covers the carotid arteries. The recurrent laryngeal nerves lie behind the lateral lobes between the trachea and œsophagus. The lower ends of the lateral lobes extend almost to the level of the sternum, the upper ends to the level of the middle of the thyroid cartilage. The gland is closely united with the larynx and trachea, so that it moves with them, rising in swallowing. The "processus pyramidalis" of Lalouette, a conical body extending up from one or both of the lobes or the isthmus to the thyroid cartilage, hyoid bone, or thyrohyoid membrane is not constant, but occurs in one-half to two-thirds of bodies examined, and varies in structure from well-developed glandular tissue to masses of cells resembling accessory thyroid glands. It represents part of the thyroglossal duct. Accessory thyroid glands occur, varying in number and place. In general they are most frequent near the hyoid bone, but they occur also on the larynx and trachea and on the aorta. They have the structure of thyroid tissue, sometimes with colloid, sometimes of more embryonic type. They have been much confused with the parathyroid glands. They are chiefly important when they undergo morbid enlargement, and will be mentioned more fully in connection with goitre. They may be supposed to functionate as other thyroid tissue, and to be capable of hypertrophy in order to compensate for loss of thyroid. Part of their supposed protective action we now know is really exerted by the parathyroids.

The blood supply of the thyroid comes from the superior and inferior thyroid arteries and the thyroidea ima (in about 10 per cent. of cases), and is relatively large, the transverse section being about equal to that of the vessels of the brain. The veins form a plexus over the gland and empty into the internal jugulars or brachiocephalic; they are without valves. The lymphatics begin in lymph spaces around the vesicles, or as fine channels that penetrate between the epithelial cells as far as the colloid, form rich anastomoses, and finally pass through the superior

and inferior deep cervical glands. The nerves rise from the inferior and middle cervical ganglia, and the superior laryngeal nerve. They accompany the bloodvessels and end partly on the latter, partly on or between the epithelial cells of the follicles.

The weight of the thyroid varies much according to age, but also according to locality. In the United States, Wells found the weight in persons over forty-five years, 16 grams; between twenty and forty-five years, 25 grams. Thyroids of 50 grams weight or more have been found with normal histological appearance. The gland is larger in women than in men; relatively larger in infants than in adults (1 to 700 to 1000 of body weight compared with 1 to 1500 to 2200). On the average the right lobe is larger than the left. The absolute measurements are, on the average: Transverse, 50 to 60 mm.; length of lateral lobes, 50 mm.; height of isthmus, 5 to 15 mm.; thickness of lateral lobes, 18 to 20 mm.; of the isthmus, 6 to 8 mm.

Development.—The thyroid is derived from a median anlage in the ventral wall of the pharynx. The derivation of the lateral lobes from the fourth branchial clefts is generally abandoned. The fetal thyroglossal duct becomes obliterated in the fourth month, the foramen cecum of the tongue indicating its mouth.

Structure.—The surface is smooth and the consistency soft, but harder in the bloodless organ; the color is reddish-brown. The gland is enclosed in a fibrous capsule which sends septa of various sizes into the interior. It is made up of follicles, round, tubular, sacculated, prismatic, or branching, from 15 to 150 microns in diameter. The follicles are lined with columnar or cubical cells, which rest upon the blood and lymph vessels without any membrana propria. Some vesicles are without lumen, others contain the so-called colloid. This begins as fine granules, which become larger and finally leave the cells and form the contents of the vesicles. Desquamated epithelial cells, red blood corpuscles, and blood pigment, often occur in the colloid. In the latter are also found clear spaces, so-called vacuoles. Some of these are doubtless artefacts. The colloid becomes thicker and stains more intensely with its stay in the vesicles. The differences in composition give different histological pictures. If thin, it stains less intensely in general, and better with eosin or picric acid than with hematoxylin or acid fuchsin. If very thin, fixing solutions produce granular appearances of fibrils or meshworks, that cannot be produced by the same methods in all thyroids, and so are not wholly artefacts. In the septa lie the blood and lymphatic vessels and nerves. The lymphatics are noteworthy because they often contain colloid or a substance with similar optical and staining qualities. The colloid enters the general circulation through lymph vessels which penetrate into the follicles (Matsunaga). Between the follicles epithelial cells can often be found singly or in groups. They are sometimes supposed to be embryonic remains, but they do not seem capable of taking up active development on extirpation of part of the gland.

Chemistry.—The most important chemical feature of the thyroid at present is the iodine content of the colloid material, discovered by Baumann in 1895. The iodine exists in an organic compound, "iodothyrin," or

"thyroiodine," in which iodine is present in proportions of 9 per cent. or more (14.29 according to Oswald). The actual amount of iodine in a single gland varies from 2 to 9 mg. The iodothyrin in turn is combined with a protein called "thyrogen" by Blum. Oswald showed that colloid contains a mixture of albuminous bodies, and he distinguishes the iodine-containing "thyroglobulin" and a nucleoprotein, thyro-albumin, free from iodine, but rich in phosphorus. There are remarkable differences in the amount of iodothyrin present in thyroids of different kinds. It is present in average amounts in the newborn. It varies remarkably in total amount in thyroids in different parts of the world. Baumann thought the iodine content less in goitrous districts, but Oswald showed that in goitrous glands the average is higher, the amount in individual cases being as high as 50 to 100 mg. In non-colloid goitres iodine may still be present.[1] It is diminished in general disease and in menstruation; it is stored up in the body during pregnancy.

Various albumins, cholin, lipoids, and a lipolytic ferment have been found in the thyroid. Specific ferments have been obtained by Abderhalden's method (Bauer, Lampé, Singer).

Function.—Our knowledge of the function of the thyroid began with the observations of Gull (1873) and Ord (1878) on the disease now known as myxœdema, and the observations of Kocher and Reverdin (1882, 1883) on cachexia thyreopriva or cachexia strumipriva.

The thyroids are essential to life. If they are wholly removed, death occurs with cachectic symptoms. If part (one-sixth, Beresofsky) of the gland is left *in situ* or transplanted into another part of the body, or if accessory thyroids capable of hypertrophy are left behind, or if thyroid substance or its active principle be ingested, the consequences of removal will be less severe, or may be escaped entirely. Such regeneration, or compensation, for probably both are concerned, is more likely to occur in young animals, as shown by Wagner, Horsley, Breisacher, and others, and the resulting changes will depend partly upon the youth of the subject.

Two opposite sets of symptoms follow from diminished and excessive thyroid activity respectively. With diminution, growth is lessened. In the young animal not only is macroscopic growth diminished, but cells fail to reach their proper development and the connective tissue remains myxomatous. The skin and hair show impaired growth. The nervous system undergoes degeneration and its function is impaired, as shown by psychic, motor, and sensory disturbances. The heat regulation, metabolism, and gaseous interchange are all depressed. The results of lessened activity of thyroid function will be more fully dealt with in connection with myxœdema and cretinism. Excessive activity of thyroid function, produced experimentally by feeding with suitable preparations, is shown by excessive metabolism, decrease of weight, not only from destruction of fat, but also of proteins, increased growth of long bones in young animals, and various nervous symptoms, affecting the heart (palpitation and tachycardia), the central nervous system

[1] See Marine, *Johns Hopkins Hospital Bulletin*, 1907, xviii, p. 359.

(irritability, sleeplessness), and the peripheral nerves and muscles. Glycosuria is not rare. These conditions will be discussed in detail in connection with Graves' disease.

The present conception of thyroid function is that the action is chiefly exerted through a secretion, thyroglobulin, which acts as a hormone. The hormone may be compound, with special affinities and activities. At present we can recognize only effects on many organs and tissues, some stimulating, some inhibiting, but we do not know whether the hormone action is direct or exerted through the nervous system.

The Colloid Matter.—It has been mentioned that our knowledge of the formation of colloid is incomplete. More than that, there are no infallible microchemical or fixing and staining methods by which we can recognize colloid. Wooley suggests that the non-diffusible colloid may be converted into the crystalloid form in various ways.

As regards the iodine, we now know that iodine is not restricted, in the body, to the thyroid. According to Bourcet, $\frac{1}{3}$ mg. is ingested daily by human beings, in food. In man it is found in all the organs, especially the thyroid of adults, the adrenals, muscles, parathyroid, hypophysis, central nervous system, thymus, spleen, lymph glands, liver, and kidney. It has been found in cell nuclei. In all other organs it is always in very much smaller amounts than in thyroid. In hair and muscle the amount increases with the ingestion of iodine. In the thyroidectomized dog iodine can still be found.

We have no way of recognizing either the richness in iodine or the amount of colloid during life except by its effects, and the experimental findings are very contradictory. Full vesicles and colloid in lymphatics (or in veins or arteries) are not proof of active secretion. In the newborn there is little or none, and although it may be said the function has not yet developed, the thyroid of Graves' disease also contains little, although a hyperfunction is generally admitted. It is obvious that storage, on the one hand, and rapid exit, on the other, may account for some of the discrepancies. In Graves' disease the rapid flow of blood through the gland may assist in keeping the latter relatively empty. A similar explanation can be made for acute infections, in which, as autopsies show, the vesicles are also often found empty. Thick colloid is probably evidence of long stay in the gland, but we do not know whether such colloid is either more or less concentrated as regards its essential constituents. A. Kocher has shown that some non-functioning goitres may be full of colloid. In short, the presence or absence of colloid is no criterion of the intensity of thyroid function. The latter may be supposed to depend rather upon the amount of production and the rapidity with which the secretion leaves the gland. Lücke has shown that the activity of secretion is governed by the nerves. It is uncertain whether thyroid secretion is continuous or periodic, but the latter seems more probable.

The true nature of "iodism" and "thyroidism" have not yet been cleared up by the numerous investigations of thyroid functions and of iodine in the body. Iodine in other forms does not act like thyroglobulin in oxygen and nitrogen metabolism in health, or in obesity and myxœdema.

"Iodism," so-called, as Lebert suspected, is more likely a thyroid intoxication, and will be mentioned more in detail in connection with goitre. Reid Hunt has made some suggestive investigations in regard to the thyroid secretions. Roos thought there was a relation between the amount of iodine and the physiological activity of the thyroid. Oswald thought iodine essential to the activity of the thyroglobulin. Hunt asserts: (1) That the physiological activity of thyroid, as tested by poisoning by acetonitrile and morphine, varies directly with the percentage of iodine. (2) Iodine-free thyroid has a low degree of physiological activity. (3) This can be increased by adding iodine to it, or by taking up iodine in the body.

As Hunt says: "It seems possible that a thyroid may be ineffective either by producing too little of the normal iodothyroglobulin, or by producing a thyroglobulin too poor in iodine. It also seems possible that the thyroid may meet increased demands in various ways: by an increase in the percentage of iodine, by an increase in the iodine-free constituents, or, most advantageously, by an increase of both. In addition, it may be supposed that in some conditions there is a more rapid circulation of iodine." Kraus points out that the results in Hunt's experiments may be due to the increased metabolism induced by the thyroid secretion, setting more sulphur free to combine with the toxic substance. It is very doubtful whether thyroglobulin represents all the active substances of the thyroid, even if we believe it the most important in many respects.

Other Relations of the Thyroid Gland.—Its close relation with the reproductive organs is shown by the (congestive) enlargement in menstruation and pregnancy; the greater demand for thyroid secretion during pregnancy, as shown experimentally by Halsted; bitches with partial thyroidectomy, free from symptoms, gave signs of athyrosis while pregnant and recovered after littering. It is possible the thyroid enlarges in pregnancy in order to supply the fetus, which does not yet contain iodine in its thyroid. That there is a relation between the thyroid and the kidneys is believed as the result of certain observations in eclampsia. Blum observed nephritis in thyroidectomized dogs. The atrophy of the thyroid in old age may be the result of the decline of the sexual life. The thyroid arteries are said to become sclerosed relatively early.

The red blood corpuscles decrease after thyroidectomy. This is not now looked upon as evidence of blood forming powers on the part of the thyroid, but rather as the result of increased destruction of blood by toxic substances or the deficiency of the activity of the blood-forming organs from one or the other effect. The coagulability of the blood has been found low in cases of hypothyroidism (Bauer).

The experiments, in regard to cytolytic or cytotoxic thyroid serum, of Mankovsky, Gontscharukof, Yates, MacCallum, and Portis need not be detailed here,[1] although they promise further additions to our knowledge of thyroid physiology. Carrel's cultivation of thyroid tissue *in vitro* promises important experiments in future.

[1] Milton M. Portis, *Journal of Infectious Diseases*, January, 1904, i, 127 to 139.

CONGESTION OF THE THYROID GLAND.

The large size of the thyroid vessels, their rich anastomoses, and the rapid flow of the blood through them, all tend to produce changes in the amount of blood in the gland at various times. This means, of course, that congestion is easily brought about, but it is important to remember that this is not merely such a congestion as may occur in any gland, from secretory stimuli. Ewald well speaks of the thyroid as a cavernous organ, a view held by Graves.

The tendency of the thyroid to swell in some persons, from emotional excitement, posture during sleep, the wearing of tight collars, during epileptic fits, from carrying loads on the head, forcible expiration, holding the breath, long since caused the thyroid to be looked upon as a safety reservoir for the brain. The popular and scientific literature on congestion of the thyroid from irritation of the sexual organs—more accurately speaking, the female sexual organs—is enormous, but by no means complete. Menstruation, coitus (especially defloration), masturbation, pregancy, and confinement have all been observed to be associated with temporary swelling of the thyroid. It is not known, however, whether this is a congestion or, at least in some of the cases, hyperplasia or hypersecretion, with temporary excess of colloid in the gland. Forneris reported an increase of 3 cm. during sleep, subsiding in a quarter of an hour upon waking, which could hardly be explained otherwise than by congestion, but this cannot be accepted for all the other cases.

Congestion is often more conspicuous in the goitrous thyroid than in the normal, and although it has been supposed at times that some goitrous enlargements were purely vascular, this is no longer believed. However, even a small goitre, especially in Graves' disease, may have an excessive development of vascular tissue, so that this element predominates on physical examination. While there are reasons for believing that congestion of the thyroid favors the development of goitres, a rapidly developed swelling of the gland, sometimes assumed to be congestive, is often the actual beginning of a goitre. In many cases, also, a condition thought to be congestion of the thyroid may be the congestion with other changes of an inflamed or degenerated gland, as described below.

On account of the facts just stated a diagnosis of congestion of the thyroid should only be made with the greatest reserve, and cases suspected to be of that kind should be carefully followed up with reference to the possibility of inflammation, goitre, Graves' disease, or malignant disease.

Congestion of a normal gland from temporary causes is usually not a matter for *treatment*. If it occurs often, the causal factor should be ascertained if possible. Congestion associated with infection, intoxication, traumatism, or inflammation should be treated as part of the chief condition.

THE EFFECTS OF TOXIC AND INFECTIOUS PROCESSES IN THE THYROID.

Thyroiditis.—Classification.—No satisfactory classification of the toxic or infectious diseases of the thyroid can be made at present. An etiological

classification is still inaccessible, because even when the thyroid affection follows a disease of known etiology, such as influenza, it may be due to a different infection, the exact nature of which cannot always be determined. A division into "toxic" and "infectious" processes is equally beyond our present knowledge. The distinction between "simple" and "purulent cases" is important clinically, but neither sufficient nor accurate pathologically.

For the present it will suffice to speak of the various causal factors, using the term thyroiditis for both toxic and infectious cases.

Etiology.—*Age and Sex.*—Most cases reported as thyroiditis occur between the twentieth and fortieth years. The processes following infection will of course fall in the period at which those diseases chiefly occur, often in early life. The statistics at present show a slightly greater number of cases in females. Epidemics of simple thyroiditis have been reported by Brisson and Demme. The cases of the latter followed measles.

As *predisposing* causes, everything that may lead to congestion must be admitted. Among these we find trauma, including strangling attempts and the carrying of heavy loads upon the head. The "cold" and "rheumatism" of earlier times will be recognized now as infections of obscure but undoubted microbic nature.

Exciting causes may be bacteria, or poisons from without, such as alcohol, or poisons formed in the body. Chagas, in Brazil, describes cases due to parasitic flagellates. The microbic cases are called primary when the disease begins in the thyroid, secondary when the thyroid becomes involved after disease makes itself manifest elsewhere.

Among infectious diseases accompanied or followed by thyroiditis are typhoid fever, smallpox, scarlet fever, measles, diphtheria, cholera, influenza, acute rheumatic fever, various infections of the nose, pharynx, and tonsils, erysipelas, puerperal fever, and malaria. In many cases cultures are negative; in some, with known causes, bacteria have been found in the thyroid different from those of the primary disease. Caccia has reported a streptococcus abscess in the thyroid of a twenty-two months' old child, which began eighteen days after vaccination. The latter had severe local and general reactions. From observations of Combe and Rie, it seems that infections during pregnancy may affect the thyroid of the fetus.

Besides the cases recognizable clinically as thyroiditis, many cases have been recorded in which the anatomical changes of thyroiditis were present, although in milder forms. These can be spoken of as toxic thyroiditis or toxic degeneration of the thyroid. In acute infections, such as scarlet fever and smallpox, less so in measles, there are marked hyperplastic alterations, with hyperemia, increase of colloid in the lymphatics, and arteritis or phlebitis with thrombus formation. In diphtheria the change is not constant. Small size of the vesicles, desquamation, and absence of colloid have been observed. Similar changes have been found in pneumonia, sepsis, osteomyelitis, erysipelas, purulent peritonitis, etc. In tuberculosis Roger and Garnier, Torri, and de Quervain have found sclerotic processes in the stroma. Torri found the connective tissue

myxomatous. Alcohol probably causes similar changes. In many bodies with a history of alcoholism there was also other disease that could have affected the thyroid. Cachectic diseases, like cancer, diabetes, nephritis, Addison's disease, do not seem to affect the thyroid as distinctly as do the others mentioned. Besides alcohol, as an example of a poison from without, phosphorus can be considered a thyroid poison on the ground of animal experiments. Iodine may be capable of exerting a toxic action on the thyroid, but our knowledge in that respect is very scanty.

The question is important, whether the effects on the thyroid by toxic substances, either of bacterial origin or otherwise, are due to the irritating action of the poisons on the gland, or to compensatory processes set up in the organ in order to combat the toxic material. This question depends for its solution upon the real nature of the thyroid function.

Pathology.—Thyroiditis can be classified anatomically as simple or purulent, and each of these can be subdivided into parenchymatous, interstitial, or diffuse.

Simple Thyroiditis.—Inflammation of more than the mildest degree sooner or later affects the connective tissue and vessels, but in most simple inflammations the parenchymatous changes are more marked, and much alike even when the causes are different. The epithelial cells project into the lumen of the vesicles or desquamate, filling the lumen more or less completely. At the same time there is increased growth of cells from the walls. The colloid becomes more liquid, and shows in hardened specimens granular material, vacuoles in large numbers, and often a stringy or meshwork appearance. Complete disappearance of the colloid is often noted. While granular or fibrillar changes are due to fixation, they are more marked than similar hardening solutions ever produce in normal colloid. The colloid also stains better with acid dyes, such as eosin or picric acid, than with hematoxylin or acid fuchsin. The desquamation of epithelial cells is only the exaggeration of a normal process, and occurs in other pathological conditions, such as congestion, intoxications, and infections.

In the vesicles, and also in the interstitial tissue, round or polynuclear cells occur, and de Quervain also found foreign body giant cells. The changes in the connective tissue show various stages of infiltration, going on to new formation. The bloodvessels share in the inflammatory process. The lymphatics are also concerned, and, besides the ordinary changes of inflammation, show colloid or colloid-like material in various amounts.

It is not always easy to make a histological diagnosis between acute thyroiditis and some goitres. In case the greater part of the gland is involved, a careful comparison will usually show points of difference as compared with various forms of goitre, but if the process is focal it may be impossible to decide the question.

Purulent Thyroiditis.—Purulent thyroiditis is rare, but sometimes follows pyogenic infections. Weil saw a case with a pure culture of typhoid bacilli four years after typhoid fever. It may begin in the vesicles or in the connective tissue. The abscesses may be single or multiple, may be small, without severe phenomena during life, or may

be large and cause such processes as are described below among the complications of goitre.

Symptoms.—In cases of infectious thyroiditis there is no constant relation between the primary disease and the form or severity of the thyroiditis. This is especially true of the cases occurring after pharyngitis or rheumatic fever, which have often been mild, but sometimes severe, as in a case reported by Illoway.

The clinical features usually begin suddenly, with chills or chilly feelings and the other subjective symptoms of an acute fever. By the end of the first day or at the latest the second day there is a sensation of fulness in the throat, and at times difficulty in swallowing. With the feeling of fulness there is often a characteristic pain, radiating to the ears, occipital region, and teeth, or even to the shoulders and chest. Such a pain is present at times in cases of malignant goitre, and in persons who undergo thyroidectomy without general anesthesia. By the second day there is a swelling corresponding to the part involved. In acute infectious diseases without marked evidence of thyroiditis (scarlet fever) Garnier found an increase of 1 to 2 cm. in the circumference of the neck. The swelling is usually one-sided, the right lobe being affected more commonly than both sides, less frequently the left lobe alone, the isthmus very rarely. The swelling may begin in one lobe and gradually spread so that both sides are involved at once, or it may subside in one and then appear in the other. The size of the swelling varies greatly. The gland is hard, as a rule, sometimes elastic, rarely doughy in simple cases. It moves with the thyroid cartilage and trachea in breathing and swallowing. The skin over the tumor is sometimes not altered in color, but in severe cases it is red, with swollen veins, and sometimes œdematous. In a case of erysipelas the redness began over the thyroid swelling and spread from there. The affected gland is tender on pressure. Subjective sensations are slight in mild cases, but in others there is, in addition to the symptoms mentioned, dyspnœa, fulness of the head, headache, dizziness, even delirium. Hoarseness is sometimes present, due to an implication of the recurrent laryngeal nerve or an associated laryngotracheitis. Epistaxis sometimes occurs. According to the seat and extent of the swelling, there may be congestion or cyanosis of the face, enlargement of cervical veins, displacement of neighboring organs, and interference with the movement of the head and neck from pain in or pressure on the muscles. Irritation of the sympathetic nerve may produce ptosis, miosis, or cessation of perspiration. Difficulty of swallowing may be so severe as to require artificial feeding. The temperature and pulse are usually only moderately affected, unless by the associated or primary disease.

Course and Outcome.—Simple thyroiditis usually subsides in a few days or a week at most. Relapses sometimes occur, or delayed resolution, so that the course may be several weeks or months, and the gland finally resume its original size. Resolution may occur even when the swelling and local and general symptoms have been most severe. Suppuration occurs in a large proportion of severe cases. In such cases the temperature is higher, chills may be repeated, redness and swelling become more pronounced, œdema or fluctuation develops in circumscribed or diffuse

form. In such cases rupture may take place externally or into the trachea, œsophagus, or mediastinum. "Dissecting thyroiditis" sometimes occurs. Gangrene is a rare result of thyroiditis; after extensive destruction healing may occur without loss of function. Death sometimes occurs from thyroiditis, either from asphyxia from compression or from rupture, or from exhaustion due to severe infection. Iodine, even in dressings, increases the severity of symptoms.

Remote Effects.—An important question for the future to solve is the relation of thyroiditis to myxœdema and Graves' disease. Remlinger has reported a case of acute myxœdema which may have had such an origin. It is well known that Graves' disease often begins with symptoms that suggest an acute thyroiditis or strumitis, and when we consider the mild symptoms of many cases of thyroiditis in acute infections it seems likely that not a few cases of so-called primary Graves' disease may have had their origin in that way.

Diagnosis.—This depends upon the recognition of the symptoms and the physical signs of the disease. Congestion, hemorrhage, goitre, malignant disease, also syphilis and tuberculosis, must be considered in the differential diagnosis. Other tumors of the neck, perhaps aneurisms, may have to be excluded. Congestion and hemorrhage can usually be distinguished by the absence of fever and general symptoms, and the local peculiarities. Goitre, especially acute goitre, may be impossible to distinguish at first, but the history, the possibility of detecting an infection or intoxication, the endemic occurrence of goitre, will soon serve to make a correct diagnosis. Riedel, Tailhefer, and Heineke have reported cases of chronic induration in which the differentiation from malignant disease was impossible. In such cases excision should not be delayed, but the diagnosis should be based upon the results of the examination of the excised gland. In all cases the course of the disease is important to follow. In all severe cases early and thorough use of the exploring needle, with aspiration, under complete aseptic precautions, should be practised. In one case of Breuer's, although the process seemed simple, there was a staphylococcus abscess in the gland.

Prognosis.—This must consider the near and remote outcome. The former is usually in proportion to the severity of the clinical phenomena. The latter cannot be determined in any case, but patients who recover should be advised about the need of careful examinations whenever symptoms of any kind occur in future.

Treatment.—In simple cases rest, mild diet, attention to the bowels and to other symptoms that may be present, and, locally, an ice-bag usually suffice. Counterirritants, poultices, and massage should be avoided. Antipyretics are not indicated, but salicylates can be used in pyogenic or rheumatic cases; quinine in malarial cases (with parasites in the blood). Morphine or hypnotics may be advisable. Suppurative cases should be treated surgically, by incision, with or without drainage, according to the condition. Aspiration should not be used for treatment in such cases.

Tuberculosis.—The occurrence of tuberculosis of the thyroid gland was formerly considered rare, but since the investigations of Chiari (1878) it

has been shown by many writers that in tuberculous individuals the thyroid is frequently involved (Chiari, 6 per cent.; Fränkel, 10 per cent.; Hegar, 3.6 per cent. in 1563 cases), though the relative proportion suggests a local immunity.[1]

The commonest form is miliary tuberculosis. This occurs in all cases of general miliary tuberculosis, and also in other cases. It affects a part or all of the gland. The latter is rarely enlarged. Degenerative or productive changes take place to a slight degree around the tubercles. In the chronic fibroid induration of the thyroid, described by Roger and Garnier,[2] in tuberculous subjects, tubercles and tubercle bacilli are not to be found as a rule. The authors ascribe the sclerosis to a primary degeneration due to toxins carried by the blood.

Nodular tuberculosis is rarer than the miliary form, but much more important clinically. It may with much reason be called struma tuberculosa.[3] Arnd[4] has collected 44 cases that seemed primary. Many were discovered by accident. Hedinger[5] reported finding tubercles in 10 out of 608 benign goitres. The thyroid is enlarged, causing a tumor externally. This, from its hard, nodular character and its rapid growth, has often been mistaken for a malignant process. In other cases the mass grows internally, sometimes causing compression and stenosis of the trachea. On section, nodular tuberculosis of the thyroid shows tuberculous tissue in various stages. Compression and interstitial inflammation of the neighboring glands occur in varying degrees. Calcification sometimes occurs in the sclerotic connective tissue. The caseation may be in small foci, or sometimes in large quantities (60 grams in a case of Schwartz). Schiller found iodine in the tuberculous pus. Bacilli are usually scanty, or may escape the most thorough search, even when the histological picture is typical. In some cases the tuberculosis grows in an old goitre.

On account of the impossibility of distinguishing the nodular form of tuberculosis, the grave suspicion of malignancy, and the possibility that if tuberculous the growth is primary or that it may break down and form large cavities, extirpation is always indicated. In case the growth causes tracheal stenosis, or pressure on nerves, extirpation should be done. In some cases there are symptoms of Graves' disease.

Actinomycosis.—Actinomycosis of the thyroid has been observed. Koehler[6] saw a case in which a woman, aged twenty-five years, a dairy hand, had characteristic ulcerating actinomycosis for nine months, part of the time under treatment, before he did a radical operation followed by transplantation. Symptoms of myxœdema began three months after the onset, and became pronounced, but subsided after the operation.

The proper *treatment* of such cases is surgical. Potassium iodide may be used in addition, internally as well as in local or parenchymatous injections.

[1] See Pollag, *Beitr. z. klin. d. Tuberkulose*, 1913, Band xxvii, Heft 2.
[2] *Archives gén. de méd.*, 1900, vol. clxxxv, n. s. iii, p. 385.
[3] Bruns, *Beit. zur klin. Chir.*, 1893, x.
[4] *Deutsch. Zeitsch. f. Chir.*, 1912, cxvi, 7.
[5] *Ibid.*, p. 125.
[6] *Berl. klin. Woch.*, 1894, p. 927.

Syphilis.—The recognition of syphilis of the thyroid is comparatively recent, the most authoritative work being that of Engel-Reimers,[1] who observed swelling of the thyroid in half the cases of recent infection. Women were more frequently affected, in the proportion of 56 to 45. The swelling begins early, in the secondary incubation stage or during the period of secondary rash. It is soft and painless. Specific treatment has very little effect, the swelling going down very slowly. Mauriac saw the enlargement of early syphilis subside quickly in one case.

Gummata sometimes occur; Davis[2] collected 20 cases from the literature. In tertiary syphilis the process may involve the whole thyroid gland, and may be associated with symptoms of Graves' disease (Demme) or myxœdema (Koehler). As in tuberculosis of the thyroid, syphilis sometimes has a rapid growth, and may simulate malignant disease. Pain or dyspnœa, from pressure on the trachea or the recurrent laryngeal nerves, may occur. Perforation into the trachea has happened. In a case reported by Clarke, an ulcerating gumma of the isthmus caused œdema of the glottis, requiring laryngotracheotomy. Recovery followed.

Diagnosis.—The diagnosis of syphilis of the thyroid presents no difficulty when there is a clear history or other evidences of the disease. Late isolated lesions or congenital cases are much more difficult to recognize, and the former can usually not be diagnosed without histological examination.

Treatment.—Specific treatment is of course to be used if a diagnosis or even probable diagnosis can be made, but time should not be lost before advising surgical treatment, in case there is not positive improvement.

Echinococcus.—Echinococcus of the thyroid is rare, even in countries where the disease is frequent in general.[3] Infection usually takes place through the blood, but in one case (Meinert) it was supposed to be due to the licking of a wound in the patient's neck by his dog. Simple and multilocular cysts occur, with the secondary and degenerative changes common to echinococcus elsewhere.

Symptoms.—The course is chronic. The symptoms are slight at first, and the process resembles cystic goitre in its chief clinical features, and is usually so diagnosed. Hydatid thrill is rarely observed. Urticaria is frequently present when the cyst decreases in size. Compression of the trachea may occur, as with other kinds of enlargement of the thyroid. Suppuration and necrosis are not unusual. O. Ehrhardt reported a case of retrosternal echinococcus cyst in which it was impossible to tell whether the infection began in the thyroid and grew down, or in the mediastinum, becoming adherent to the thyroid.

Diagnosis.—The diagnosis is rarely possible without puncture and examination of the contents of the cyst.

Prognosis.—The prognosis is unfavorable. Perforation may occur at any time. According to von Eiselsberg, 4 out of 18 patients died, although the cysts were not larger than an orange.

[1] *Jahrb. der Hamburgischen Staatskrankenanstalten*, 1891–92, iii, 430.
[2] *Archives of Int. Med.*, 1910, v, 47.
[3] Vitrac, *Revue de chirurgie*, 1897.

Treatment.—The treatment is operative, by extirpation or partial thyroidectomy. Puncture with or without medication should never be used for therapeutic purposes in such cases.

Tumors.—Histologically, as well as clinically, it is always difficult, sometimes impossible, to distinguish the various forms of benign goitre from malignant newgrowths. This difficulty explains the fact that our knowledge of the subject is very recent. The real history of sarcoma of the thyroid began with the work of Kaufmann, in 1879. Morf collected 40 cases in 1899; Lartigau, 15 more in 1901; Ehrhardt,[1] in 1902, raised the number to about 100, and at the same time collected the histories of about 150 cases of carcinoma. Benign connective tissue neoplasms, fibroma and lipoma, are so rare as to be without clinical interest. The "fibromas" described by Delore and Ricard were probably sarcomas. Benign epithelial tumors of the thyroid gland have been well described by D. Marine.[2]

All kinds of malignant thyroid tumors occur more frequently in goitrous regions and in persons with previous goitres. In Bern, Limacher found sarcoma 44 times and cancer 38 times in 7461 autopsies. Chiari, in 7700 autopsies in Prague, found only 5 sarcomas and 11 cancers.

Both primary and secondary tumors occur. Sarcoma of the thyroid occurs sometimes in early life, as it does in other regions, but there is an unusual tendency for it to occur late in the subjects of goitre, the sixth decade being most frequently concerned. Cancer of the thyroid is most frequent between forty and sixty, but sometimes occurs in early life. Men are less frequently affected than women.

The combination of sarcoma and carcinoma of the thyroid is rare, but sarcoma of a goitrous gland sometimes produces the picture of sarcoadenoma or sarcocarcinoma. Saltykow[3] has reported such a case in which he believed the sarcoma was the original tumor, carcinomatous change then occurring, to produce not a mixed tumor, but two tumors, in an already goitrous gland. A similar view has been advanced by Woelfler.

Carcinoma of the thyroid occurs in several forms, sometimes easy to distinguish, but often not. The most frequent is the medullary (alveolar cylinder celled) carcinoma, in which alveoli of various sizes and shapes occur, with proliferation of epithelium. The alveoli contain colloid material. The stroma has the usual characteristics. Sometimes cysts occur, and these are occasionally papilliferous. Congenital cystadenoma has been observed.

Adenocarcinoma of the thyroid sometimes produces histological appearances like those of medullary cancer, but more frequently it is adenomatous, having the type of adult or fetal thyroid tissue. In the latter case there are solid strands of epithelial cells in which neither follicular structure nor colloid are present. The connective tissue contains few nuclei; the bloodvessels are usually abundant. Sometimes the newgrowth is circumscribed, sometimes it resembles a local or diffuse hypertrophy of normal gland tissue.

[1] *Beiträge zur klin. Chir.*, Band xxxv.
[2] *Jour. of Med. Research*, 1913, xxvii, 229.
[3] *Centralbl. f. allg. Pathologie und path. Anat.*, 1905, p. 547.

Scirrhus of the thyroid is very rare. It has occurred in young patients (twenty-six years in a case of Billroth's). Like adenocarcinoma, it may exist without enlargement of the gland, the central part being made up of dense scar tissue, the peripheral growth scanty.

Malignant tumors of the thyroid usually produce enlargement, which may be slight or may equal the size of an adult head. The right lobe is affected oftener than the left. The enlargement is smooth or lobulated, usually firm or hard, sometimes soft. It may be cystic and fluctuating, or vascular, and in the latter case, pulsating. It is usually translucent and glossy on section, sometimes granular, sometimes, in cancer, distinctly alveolar. The color is yellow or yellowish red.

Besides the regionary involvement, *metastasis* of thyroid tumors is very important. It may occur before local invasion, and in some cases causes all the discoverable clinical features. It takes place by the veins or lymphatics, or both, but in cancer venous metastasis is relatively common, owing doubtless to the vascularity of the gland. The relatively slight participation of the lymphatics has been explained by the resistance of the capsule. However, carcinoma of the thyroid produces lymph gland involvement in about one-third of the cases, sarcoma in about one sixth. The organs most affected by metastasis are the lungs and bones, less frequently the liver, kidneys, and pleura. Of the bones, the skull, inferior maxilla, and sternum are most often affected; the long bones of the extremities and the pelvis next. Gierke, and also Ribbert, have discussed this predilection. The metastases of thyroid cancer are also remarkable for their histological peculiarities. Thus, a carcinoma may have metastases containing normal looking thyroid tissue (also containing iodine).

Symptoms.—Both sarcoma and cancer of the thyroid may remain within the capsule for relatively long periods, causing symptoms like those of goitre, or, if rapid, those of thyroiditis or strumitis. The skin may long remain free from adhesion.

After invasion through the capsule or metastasis has occurred, the symptoms depend upon the direction taken and the seat of the metastasis more than upon the variety of tumor. Difficulty in swallowing from pressure upon or growth into the œsophagus sometimes occurs before dyspnœa, which may be due to pressure upon the trachea or involvement of nerves. Sometimes the tumor fails to follow the trachea in swallowing. Erosion into the œsophagus, larynx, or trachea may occur. Congestion of the veins in the neck is frequent, and malignant thrombosis sometimes occurs in such vessels. Œdema of the face and neck sometimes occurs. Hoarseness occurs from the implication of the laryngeal or tracheal mucosa, or of nerves. Sometimes malignant vegetations form inside the trachea, and may lead to a diagnosis (tracheoscopy). Perforation and ulceration of the skin are rare. Pressure on the nerves usually occurs relatively late, and may cause increase of dyspnœa and cough without expectoration. If the sympathetic is affected, there may be slight exophthalmos, miosis, loss of pupil reaction, and tachycardia. Paralysis of the arm has occurred. Pain in the occiput, ear, and shoulder sometimes comes on early. The course of sarcoma of

the thyroid is usually short—from a few weeks to a year and a half, one year being the average duration. In medullary cancer the course is even shorter. In adenocarcinoma it may be very slow.

Among the *complications* may be mentioned especially perforation, necrosis, or hemorrhage from the larynx or trachea. Woefler saw a case of sarcoma in which malignant thrombi extended down the large veins as far as the auricle. In a case of cancer reported by Hellandall, the growth eroded the sternum, caused thrombosis of the intrathoracic veins, and finally death by rupture of varicose veins in the œsophagus. Solis Cohen reported a case in which implication of the right sympathetic nerve caused unilateral spasm of the laryngeal muscles. Later, the nerves of the opposite side became affected. Death followed from pneumonia. Tillaux has reported a case in which sarcoma of the thyroid was associated with symptoms of Graves' disease. The growth was removed and recovery followed, but death occurred later from metastases in the lungs. If the whole gland is involved in the new growth, myxœdema may develop, but its symptoms are less often noted than might be expected. This may be due to the fact that in the cancerous goitre secretion sometimes continues. Remittent fever is not uncommon in the later stages of carcinoma of the thyroid. Cachexia is often absent.

Adenocarcinoma, also called malignant adenoma of the thyroid, or adenoma destruens, differs in many respects from other thyroid tumors. The gland may not be enlarged, or it may be the seat of a long-standing goitre, without recent increase of size, and without local symptoms. Metastasis may be the first evidence of the process, and especially metastasis in bone, sometimes producing solitary tumors of large size, sometimes multiple tumors. The bones chiefly involved are the parietal, lower jaw, sternum, pelvis, and humerus. The tumor in the bone may grow very slowly, lasting six or eight years. Spontaneous fracture is likely to occur. Bony union sometimes occurs, but the writer saw a case in which there was no tendency to that or to the formation of osteophytes. Oderfeld and Steinhaus report a case that illustrates the course of the disease, and makes doubtful the belief in metastasis of normal thyroid or transplantation from normal thyroid which has been widely held. In their case tumors occurred in the cranium, with the structure of normal thyroid. As the gland itself felt normal, the tumors were considered the results of a sort of transplantation. A year later death occurred from other metastases, and a small encapsulated nodule was then found in the thyroid, evidently the primary tumor, although it had normal thyroid structure. The metastases do not always resemble normal thyroid or adenoma, but may be distinctly carcinomatous, or some of them may be adenomatous, others medullary carcinoma. In this respect thyroid adenoma resembles adenoma of the liver.

Metastases of thyroid cancers may not only repeat the structure of normal thyroid, but they may even be capable of carrying on the same function. It is even possible for cylinder-celled cancer of the thyroid to produce colloid and compensate for the loss of the thyroid after extirpation. Von Eiselsberg reported an instructive case of this kind: A goitre was removed in 1886; symptoms of cachexia appeared, but

improved distinctly with the appearance of a tumor in the sternum two years later. Four years afterward pressure symptoms made it necessary to remove the sternum and tumor which was soon followed by tetany and later by cachexia. (The tetany has been explained in this case by accidental removal of an hypertrophied parathyroid gland.) The tetany slowly improved, but cachexia again appeared, and was not lessened by the growth of a tumor in the scapula. Death occurred in 1895 from marasmus. The sternal tumor was a cylinder-celled carcinoma with colloid. Von Eiselsberg rejects the idea that the carcinoma developed in a vicarious thyroid, although admitting the sternal tumor may not have been always of the same type.

Diagnosis.—The diagnosis of malignant disease of the thyroid is sometimes comparatively easy, as in case of rapid growth of a normal or, still more important, a goitrous thyroid, without symptoms of inflammation, but with involvement of skin or lymph glands or adhesion (not merely pressure on) to the œsophagus or trachea. Acute goitre sometimes closely simulates malignant disease. The writer reported a case in which a diagnosis of malignancy was made in a large indurated and rapidly growing goitre in a man aged sixty-six years. The subsequent course disproved malignancy. Such cases are always suspicious. Metastases add to the probability and usually contra-indicate treatment. The exploring trocar has been used to remove bits of tissue from the thyroid for examination. This is uncertain and should not be used.

The probability of thyroid tumor should be considered in all cases of bone tumor, and if there is an old goitre, the probability is more likely to be correct than that of primary sarcoma.

Prognosis.—The prognosis is bad on the whole.

Treatment.—The treatment is purely surgical. If there is no evidence of metastasis, a radical operation should be made with transplantation or thyroid feeding. In some inoperable cases palliative treatment (tracheotomy) is indicated.

GOITRE.

Synonyms.—Struma; guttur tumidum *seu* turgidum (Latin); bronchocele; thyrophyma; thyrophraxia; Derbyshire neck; Nithsdale neck; Kropf; Blaehhals (German); Goître, grosse gorge, gros cou (French); gozzo (Italian); papera (Spanish).

Definition.—In general, any morbid enlargement of the thyroid gland, but more strictly, as in this section, a chronic enlargement of the thyroid gland of unknown cause, with variable anatomical features, occurring as an endemic, epidemic, or sporadic disease.

For an outline of the history of goitre, the reader is referred to the first edition of "Modern Medicine," Vol. VI, p. 401.

Geographical Distribution.—Goitre occurs as an endemic, epidemic, or sporadic disease. Sporadic cases may occur anywhere. Epidemics of goitre have often been observed, usually of small extent, of short duration, and in goitre regions. In strong contrast there are places where goitre is never absent and where it often exists in a large proportion of the inhabitants, in lower animals as well as in human beings.

The classic home of endemic goitre is in the Swiss Alps. It is not uniformly distributed even there. In Piedmont it sometimes affects more than two out of three of the inhabitants. In Canton Wallis, in the valleys of the Rhone and its tributaries, and in the city of Bern it is also very prevalent. In Tyrol, Styria, the Carpathian and other mountainous parts of Austria, and in some parts of the Balkan peninsula the disease is common. In the mountains of Germany there are many foci. In France, the Alpine departments, the Vosges, Cevennes, Pyrenees, and the high central plateau are affected. In Spain, the valleys of the Pyrenees, Asturia, and Galicia furnish foci. Sweden, Norway, Finland, and the Baltic provinces have a few endemic centres. In England, besides the traditional seat in Derbyshire, Sussex and Hampshire are affected. The mountains of Asia, Japan, and many of the Asiatic islands have numerous centres. Africa has foci in Abyssinia, and there are some in the Azores and Madagascar. The early explorers of North America found it among the Indians, as Munson has in more recent times, and in Esquimos. The region of the Great Lakes (Osler, Dock, Adami) shows considerable numbers. In Mexico and the mountains of South America it is not rare. Clark and Farmer have noted a low percentage of goitre among negroes in the Canal zone.

The absolute number of goitre subjects in countries with endemics of severe degree is of great social and economic importance. In France, Mayet (1900) estimates the number as 400,000. In all the Central European countries many recruits are lost to the military service on account of goitre. In Switzerland there were 12,277 in fifteen years, according to Ewald. In France 1200 recruits annually have been exempt, out of a total of 300,000 men. The drain on the country is better expressed by the number of cretins. In Cisleithan Austria there were, in 1883, a total of 12,815, or 71 per 100,000; in one district in Styria, a proportion of 1045 to 100,000. In Piedmont, Lombardy, and Venetia there were, in 1883, 12,882 cretins in a population of 9,565,038.

In the foci in the United States and Canada the goitres are, as a rule, not large, and cretinism is rare. Adami speaks of French Canadian villages in which scarcely a family is to be found that has not one or more goitrous members. The writer found 2 to 3 per thousand of well-marked cases in an extensive investigation, and 10 per cent, in young women, in a personal examination, most of them of small size. Munson found from 1.23 to 2.36 per cent. among Indians.

Etiology.—The cause of goitre is unknown. Of the numerous factors supposed to be effective, many, such as glacier water, have been abandoned. Others may assist in the production of goitre in regions strongly affected by the disease.

Age.—Goitre is rarely congenital, and when it is, it can usually but not always be discovered that the parents are goitrous or live in goitre regions. Congenital goitre is very rare in non-goitrous districts. In Switzerland Demme found 37 cases to 642 of acquired goitre. Hyperplastic, cystic, and mixed goitres occur congenitally. They sometimes cause difficulty in confinement. Acquired goitre occurs most frequently in childhood, before or about puberty. The tendency diminishes after

the twentieth year, and cases rarely begin after forty, but a goitre acquired in earlier life may continue to grow, or may enlarge suddenly in later life, even at an advanced age. The incidence (per 1000 of population) at various periods is well shown by the analysis of Bircher, from statistics of Baillarger (13,090 cases):

Age.	Males.	Females.
0 to 10	1.8	2.2
11 to 20	7.9	11.5
21 to 30	12.6	15.4
31 to 40	11.6	24.6
41 to 50	14.0	30.4
51 to 60	12.2	29.0
61 to 70	12.3	27.4
71 to 80	6.2	19.9

Sex.—Women have goitre more frequently than men. The proportion varies up to six or eight to one, the numbers being more nearly equal in severe endemic foci. Some of the reasons given for the difference are unsatisfactory, such as the carrying of burdens upon the head, or occupations that keep the head bent forward, as in lace-making. It is more probable that some preponderance is due to the relation of the sexual organs and the thyroid and the congestion due to menstruation and pregnancy, possibly even sexual intercourse. The last, according to tradition, influences the circulation of the thyroid. In affected regions goitres frequently increase rapidly in size during pregnancy, and especially in confinement, going down rapidly in the days immediately following. Lactation has in general no effect. An increase in the size of goitres at the climacteric has been asserted, but is probably rare. Freund believed that various affections of the uterus, such as fibroma and parametritis, caused thyroid enlargement.

Infectious diseases, such as scarlet fever, are sometimes followed by goitre, but it cannot be supposed that the causes of any of the well-known infectious diseases produce many cases of goitre, and the same may be said of ordinary traumatisms, sometimes mentioned.

Goitre, in its endemic form especially, occurs in every latitude, at every altitude where people live, in various climates, on high mountains, in deep valleys, on plains at various elevations. Although the seashore is almost wholly exempt, Duncan (1905) reports as many as 20 per 1000 cases in the municipality of Macabebe, near Manila Bay, only a few feet above the level of the sea. At the same time the relation of goitre to locality has been noted always and in every place where the disease is endemic. Not only are the localities circumscribed (though not always small), but besides the natives, who become affected to a high degree, others who enter and live in such regions frequently acquire the disease, while they, as well as natives, on removing to non-goitrous localities, often recover. These conditions apply not only to human beings, but to domesticated and wild animals as well. Epidemics of goitre illustrate the local influence. They occur in goitre regions, especially in garrisons or schools, they affect large proportions of those living together, but do not spread among people living near but not in the same area.[1]

[1] See S. Taussig, *Kropf. u. Kretinismus*, 1912.

The facts that have been mentioned make it certain the cause must exist in the soil, water, or air. As regards soil, we owe to H. and E. Bircher an interesting theory of the geological relations of goitre, but investigations not only in Switzerland, but in various parts of the world have shown its inadequacy.

That the cause of goitre is ingested with drinking water is a very old and widespread belief. Vitruvius and Pliny mentioned goitre wells, and we find the latter mentioned again from the sixteenth century on. Recruits who wish to escape military service acquire goitre by drinking the water of such wells; on the other hand, families in goitre neighborhoods who drink only rain water have been known to escape; also others who drank no water, but only wine. Goitre streams or wells may also lose their qualities. Some rivers produce goitre at certain points, but not at others. Sometimes a water, previously safe, acquires goitre-producing qualities. In several places in Italy and Switzerland whole goitre districts have been much improved by the introduction of water from a non-goitrous region. Bircher shows how, in the Commune of Rupperswyl, the introduction of water from a non-goitrous region in 1884 was followed by a gradual drop in the proportion of goitrous school children from 59 per cent. in 1885 to 11 per cent. in 1895, and 2.5 in 1907.

Various mineral constituents have been found—iron, lime, magnesia—and, interesting in view of the relations of iodine to the thyroid, a smaller proportion of iodine than in the waters of non-goitrous regions. Répin has found a high degree of radio-activity in the goitre waters of the Swiss Alps, due to radio-thorium. Hesse, however, pertinently shows that among the large number of persons exposed to radium emanations, none have developed goitre.

Many authors have assigned goitre to the infectious diseases before the causes of the latter were actually recognized.

The water of goitrous regions has revealed, as does that of other places, various algæ and bacteria, but although many of these have been experimented with, none produced goitre, although the drinking of the same water has sometimes been followed by goitre in dogs and horses. It has been thought that the boiling of water lessens or checks the tendency to goitre, and the writer has seen the sequence in a number of instances of goitre in young people. McCarrison, in a series of interesting articles, has asserted the existence of pathogenic organisms in water supplies, reaching the thyroid by way of the alimentary canal. This view seems borne out by the observations of Gaylord on brook trout, but Marine, from similar observations, denies the theory and thinks a nutritional or metabolic cause more probable.

Marine has caused enlargement of the thyroid in fish by feeding, and reduced the enlargement with iodine.

The tendency at present is to a belief in an infectious origin of goitre, acquired by close and prolonged contact (Kutschera, S. Taussig), with drinking water as the usual medium. The cause may not be a single or specific one, and a toxic or metabolic origin may be effective in some cases.

Pathology.—The alteration of the thyroid in goitre is either diffuse or partial. The simplest form anatomically is that seen in mild endemic

cases. In these there is a hyperplasia or numerical hypertrophy of the glandular tissue, usually with an increase of the colloid and a proportionate hyperplasia of the connective tissue and bloodvessels. In goitre regions the thyroids of men and animals usually differ from those of non-goitrous districts, being larger, heavier, and containing absolutely more iodine. The follicles are larger, the vascularity greater.

Many of the follicles resemble those in the developing thyroid. These may be few or many, in circumscribed areas or diffuse. In the former case, termed "struma nodosa," it is difficult or impossible to differentiate between adenoma and hyperplasia. According to Virchow the hyperplasia begins in the epithelium of the normal follicles; Woelfler and Billroth derived it from the interfollicular embryonic tissue, but Hitzig's investigations confirm the earlier view. According to von Burckhardt, the so-called external capsule of the goitre, when present, is due to inflammatory processes in the perithyroid connective tissue. The internal capsule, derived from the membrana propria, is characterized by the number of its bloodvessels.

If the hypertrophy produces the gross and microscopic picture of an enlarged but normal thyroid, it is spoken of as a "parenchymatous" goitre. Such a goitre rarely reaches considerable size. A notable enlargement is almost always associated with an increase of the colloid in the follicles. As this progresses, the epithelial cells become shorter or even flat, the walls of the follicles become thinned, and may even disappear. Sometimes thin partitions can be made out in what seem at first glance to be large colloid areas. Proliferation goes on in the follicular epithelium, and both the size of the gland and the histological picture become more abnormal. Some follicles are very large, others of normal size; there are younger ones, as shown by the size and the appearance of the cells, in variable numbers. Such goitres are spoken of as "colloid."

The term "vascular goitre" is often given to growth in which the bloodvessels are disproportionately large and abundant. Such a condition is seen often in the goitres of Graves' disease, but in this the vascular enlargement is peculiar. In ordinary endemic goitres general vascular enlargement is not marked, but in some cases there are local conditions that warrant the terms "struma vasculosa," "struma aneurismatica," and "struma varicosa." In many cases of goitre, as also in malignant disease and even in the normal thyroid, there is a marked tendency to degeneration of the bloodvessels, with endarteritis, hyaline change, and calcification. These alterations have been investigated by Jores, Budde, and Farner. They are not necessarily part of a general arteriosclerotic process. Inflammatory changes, on the other hand, are rare. Amyloid degeneration occurs, but rarely plays an important part in the enlargement. Calcification and even ossification (Lücke) occur in the fibrous tissues of goitres. In all goitres various changes are likely to occur by which the size and condition of the gland become materially altered. These changes are chiefly degenerative, or the results of processes subsequent to degeneration, such as colloid and hyaline degeneration, calcification, hemorrhage, necrosis, and cyst formation.

True cysts are rare, and occur from the progressive dilatation of follicles,

or the coalescence of several follicles from atrophy of their walls. If recent, such cysts are lined by epithelium, but that is absent in old and degenerated cysts. Papillomatous growths are not uncommon in such cases. The cavities contain colloid in different degrees of concentration, often mixed with blood cells and cholesterin. False cysts occur from the rupture or necrosis of the glandular or interstitial tissue, with or without hemorrhage, followed by change in the surrounding tissue, as well as in the contents of the cavity.

The hemorrhagic cysts have been well described by W. I. Bradley.[1] He shows that the contents of hemorrhagic cysts always indicate their origin. In recent cases, or when the walls are thin, there is evidence of recent hemorrhage. When the walls are thick, or calcareous, the fluid is usually straw-colored. The walls of the cysts are fibrous, partly of new formation. They sometimes contain atrophied remains of gland tissue, as if there had been compression of the surrounding thyroid tissue, but they are not lined with epithelium. The contents consist of a thin, watery, glairy, or viscid fluid of pale yellow to purple color, containing pigment granules, leukocytes, or larger cells filled with coarse, highly refracting granules and cholesterin. Bradley ascribes the hemorrhages, whether old or recent, single or recurring, to rupture by traumatism or strain. The degenerations of bloodvessels in the goitrous thyroid make the suggestion very probable.

Fibrous goitres, so-called, are the results of chronic degenerative and inflammatory processes, sometimes nodular, rarely diffuse. Calcification is not uncommon in these. Hemorrhage is rare. Necrosis sometimes occurs. Hyaline degeneration of the connective tissue can produce the adenoma myxomatosum of Woelfler.

In long-standing goitres many or all of the changes described are present in various proportions and various stages of growth or degeneration.

Symptoms.—Onset.—Goitres are spoken of as acute or chronic. The former develop within a few hours, days, or weeks. The "summer goitres of visitors in goitre regions," epidemic goitres, and some rare vascular goitres are of this kind. They often subside as quickly as they form. Chronic goitres grow slowly, but sometimes with great and rapid variations. A sudden enlargement in a chronic goitre is suggestive of hemorrhage or malignant change.

Goitres may be important clinically either by reason of their size or by causing symptoms that have no constant relation to size, but depend on the anatomical relations of the growth. The enlargement may affect the whole gland or one (unilateral) or both (bilateral) lobes, or the isthmus (median). The right lobe is affected oftener than the left, possibly from the relation of the veins on that side. The pyramid, the lateral horns, as well as aberrant or accessory thyroid tissue may also be involved, alone or with other parts.

Size.—Sometimes the enlargement is very slight. In fact, from the range of size of the normal thyroid, it is evident that the gland may be

[1] *Jour. Exp. Med.*, 1896, i, 401.

pathologically enlarged and still be below the average size. In cases without signs of deep growth it is customary to consider as enlarged any thyroid that, in a neck of average figure, causes an appearance of swelling. Many cases of this kind are not true goitres, but depend upon temporary congestion. They are without symptoms or even cosmetic importance, or rather they add to the beauty of the neck. However, there are clinical reasons for classing such processes as goitres unless the history and course show them to be otherwise. The term "thyrocele" has no advantage as a designation for such enlargements. The goitres of ordinary classification are usually from twice to four or five times the size of the normal organ or part, but may attain enormous dimensions, hanging down over the clavicles or chest, even to the waist or thighs.

Small goitres are often unnoticed by patients. In some a tight collar may call attention to one, or it may be revealed by a sudden increase in size. The latter can often be traced to a definite cause, such as strain (confinement), trauma, an infectious disease, or an inflammatory or neoplastic alteration.

The skin over a goitre is sometimes of normal appearance, sometimes it is red, especially if the collar is too tight, or shows dilated veins under it. Cyanosis is rare. The shape of the swelling varies with the seat and the presence or absence of cysts or other localized processes. The mass moves with the larynx and trachea in swallowing. The consistency varies from a soft or soft nodular to a fibrous or bony hardness. Thrills and murmurs are very unusual even in acute goitres without symptoms of Graves' disease, in connection with which they will be described.

Aberrant Goitres.—Besides goitres occupying or springing from the usual position of the thyroid gland and growing forward, there are others of great clinical importance. Sometimes these develop in accessory thyroid tissue, and are then spoken of as accessory goitres. Often it is impossible to determine whether an aberrant goitre is a true isolated accessory one or whether it is united with the gland by thyroid tissue (false accessory goitre) or by connective tissue ("alliirter Kropf" of the Germans).

Aberrant goitres may occur in any position where thyroid tissue grows normally, or in other localities as the result of accidental conditions, such as the weight of the enlarged mass. Various classifications have been given, such as an embryonic one by Woelfler, a regional one by Madelung, and various clinical ones. In many cases, such as the submaxillary goitres, the conditions are purely surgical and need not be considered in detail here. Certain varieties are important on account of the symptoms they produce. This is especially true of lingual, retrovisceral, substernal, or intrathoracic (goitre en dedans, goitre plongeant), and intralaryngeal or intratracheal goitres. Wandering goitre and thyroptosis (A. Kocher) are interesting varieties related clinically to intrathoracic goitre. Aberrant goitre is especially important when there is no goitre in the usual position. On the other hand, if it is possible to determine the absence of a lobe or of the isthmus of the thyroid in the usual position, the symptoms may be readily explained by assuming the existence of an aberrant goitre.

Intralaryngeal and intratracheal goitres are chiefly interesting to the laryngologist. They occur with or without external goitre, as round or cylindrical sessile tumors, rising from various parts, from the posterior wall of the larynx to the origin of the bronchi. The mucosa is usually intact and smooth over the tumor, but in one case an exudate raised the suspicion of ulcer. Meerwein saw one associated with tuberculosis. It is generally believed such growths are due to embryonic remains, but Paltauf thinks they grow through the wall, and in this he is supported by Bruns. The duration of the disease is from a few weeks to fifteen years. Women have such growths four times as often as men. The age varies from fifteen to forty years. The growth is most often colloid. The subjective symptoms are those of gradually increasing dyspnœa. Laryngoscopic examination alone can prove the existence of the tumor. Bruns used thyroid extract as a differential diagnostic measure.

Symptoms Due to Pressure.—*Respiratory.*—The pressure symptoms of goitre may be classified according to the organs involved. One of the first of these is the trachea. The trachea may be flattened by the enlargement of one lobe, most dangerous being the anteroposterior flattening from pressure of an enlarged isthmus, or by enlargement of both lobes (sabre-sheath trachea), or narrowed by circular compression. The last is rare. The most serious obstruction is caused by substernal goitre. Kinking from a sudden enlargement is a dangerous condition. With any of the varieties of pressure, changes occur in the trachea and larynx—congestion of the mucosa, later hypertrophy, which may be especially marked on the vocal cords; atrophy of the fibrous or cartilaginous tissues of the trachea (Woelfler), or even softening. Tracheal and bronchial catarrhs develop in time, also emphysema. The symptoms from these changes are dyspnœa, especially on exertion, and a more or less marked stridor or cough. These symptoms vary much in intensity in different cases.

Besides the chronic obstruction there is an acute one, not always associated with chronic obstruction, due to pressure on the recurrent nerves, often spoken of as "goitre asthma." It often occurs at night, without previous symptoms, with intense subjective and objective dyspnœa. This may subside, to be repeated again and again, or may produce so-called "goitre death." More or less pressure on the recurrent nerves occurs in about 10 per cent. of cases of goitre (Woelfler), but the condition is not always severe enough to alter the voice. If there is marked pressure on one recurrent nerve the condition is dangerous, more so if both are affected. In some cases laryngospasm occurs in certain positions of the body.

Nerves.—The vagus is rarely involved in simple goitre. The sympathetic is also only rarely affected, but it may occur, with alterations of the pupils, of sweat secretion, and color and temperature of the face. The hypoglossal nerve is rarely affected, but is sometimes injured in operations, producing paralysis of the tongue. From pressure on the spinal accessory nerve spasm of the trapezius and sternocleidomastoid may occur.

Œsophagus.—Difficulty in swallowing is not frequent in benign goitre, but can occur from circular, or left-sided lingual or retrovisceral (between trachea and œsophagus) growths. There may be pain in swallowing or partial complete obstruction, so that only fluids pass. In cases of lingual goitre hoarseness and the sensation of a foreign body may be associated with difficulty in swallowing.

Bloodvessels.—Venous congestion in the neck may be due to respiratory obstruction. More directly it is due to pressure on the veins. The latter are partly pushed out of the way, but in both arteries and veins the walls of the vessels become thinned and large goitres may compress the internal jugular vein or even the jugular bulb itself. With venous congestion and cyanosis there may be a striking pallor of the skin. Œdema of the mouth or of the arms is a rare event.

Heart.—The occurrence of palpitation of the heart in goitrous subjects has long been known.

Minnich[1] gave the term "goitre heart of Rose" to the process associated with venous obstruction and distension of the right heart. In some cases it was also supposed that pressure on nerves could produce cardiac alterations; for example, pressure on the vagus may cause slight acceleration, without enlargement. The cardiac alteration due to obstruction of respiration has been called the "dyspnœic goitre heart." A. Kocher prefers to call both these forms "mechanical goitre hearts," in distinction to the true goitre heart or "struma cardiopathica." There is a great difference of opinion in regard to the nature of the latter cases. Kraus, under the name "goitre heart," describes conditions such as occur in Graves' disease, and even associated with tremor, exophthalmos (slight), and other symptoms of Graves' disease, especially of the incomplete forms. He admits the similarity of the symptoms to artificial thyroidism, but denies their relation to Graves' disease.

Minnich, whose analysis of cases is very painstaking, follows von Cyon in considering Graves' disease one of hypothyrosis, and he also thinks goitre heart is a "thyroprive" condition. Kocher does not agree with this view. His belief in the relation of non-mechanical "goitre heart" to Graves' disease, based largely upon operative experience, is shared by the majority of English and American observers. Gittermann[2] has carefully examined cases observed in his Nauheim practice, and among 121 patients with goitre and heart symptoms, 11 were distinctly cases of Graves' disease; 8 of the others had mechanical causes, venous and respiratory chiefly. The other 102, true goitre hearts, he would assign to the group of Graves' disease. In long-standing cases he found signs of myocardial degeneration.

Although the real nature and classification of goitre hearts cannot be cleared up until our knowledge of Graves' disease is more perfect, it is important now in any case to search for evidence of Graves' disease on the one hand, of pressure on the other. Kocher has properly emphasized the importance of recognizing the mechanical cases early, in order to

[1] *Das Kropfherz und die Beziehungen der Schilddrüsenerkrankungen zu dem Kreislaufapparat*, 1904.

[2] *Berl. klin. Woch.*, November 18, 1907.

give relief by operative treatment before the heart has undergone degeneration. In non-mechanical cases it is important to realize the frequent failure of digitalis. Gittermann looks upon it as characteristic of the condition.

Hemicrania has been ascribed to goitre, but chiefly in persons predisposed to headache. Pain behind the ear may be caused by the pressure of a goitre on the posterior auricular nerve. Tinnitus aurium is sometimes a troublesome symptom.

In cases with large goitres the physiognomy of the patient is often changed by the alteration of the position of the head and the shape of the lower jaw and mouth. Changes of expression from Graves' disease and myxœdema or cretinism will be discussed in other places.

Complications.—Injuries of goitres are dangerous by reason of hemorrhage from the fragile bloodvessels, but especially on account of the possibility of bacterial infection. The latter is likely to occur also in puncture of the thyroid without aseptic precautions, or by indirect infection through the blood stream. It sometimes follows injections into goitres, even when asepsis has been observed. Various pathogenic bacteria are concerned in different cases, especially pyogenic cocci, pneumococci, typhoid bacilli, and colon bacilli. The latter have been found in a patient with constipation, apparently a primary strumitis. There is usually an intense inflammation of the connective tissue, infiltrating the follicles, and going on to abscess or necrosis of greater or less extent.

The symptoms are essentially those of inflammation, with severe radiating pain in the thyroid region, chills, fever, and rapid swelling of the thyroid, with great tenderness. The skin over the inflamed part becomes red, the veins congested, and the face cyanotic. Nosebleed is not rare. From the rapidity of the swelling, compression of the adjacent organs is inevitable, with pain, spasm of the glottis, dyspnœa, and cough.

The result of strumitis is usually suppuration or necrosis. Resolution is rare. Suppuration is accompanied by softening and fluctuation, with œdema of the skin. Perforation can occur through the skin, or into the trachea, œsophagus, or mediastinum. Erosion of the common carotid artery has occurred. After perforation recovery can occur. Troizki observed a case in which strumitis followed erysipelas in a patient with Graves' disease. After perforation externally, both goitre and Graves' disease disappeared.

Diagnosis.—The diagnosis of an enlargement of the thyroid, whether general or partial, is usually easy. The shape and position of the swelling, its relation to the great vessels and the sternomastoid muscles, its movement with the larynx and trachea in swallowing all serve to prove the thyroid origin of the mass. Other tumors, such as sarcoma of lymph glands and inflammatory swelling in or under the sternocleidomastoid muscle, can usually be differentiated by their physical peculiarities, especially by the absence of upward movement on swallowing, and by the history, the blood examination, and the course of the disease.

If the enlargement is in the thyroid, the exact condition should be ascertained as early as possible. This can be done only by a careful examination of the thyroid region, of other organs, and of the history

of the case. The skin over the swelling must be examined with reference to alterations of color, presence or absence of adhesions, œdema, and enlarged veins. By palpation the consistency of all parts of the mass must be determined, and the existence of thrill and the presence of adhesions to other structures. In palpation it is important to examine with the patient upright as well as lying down, and to use both hands, so as thoroughly to outline the mass, to prevent it from slipping, and to get an accurate idea of the consistency. Auscultation is important on account of possible vascular murmurs, or stridor not otherwise detected. The larynx and trachea should be examined by the laryngoscope, to detect possible stenosis, congestion, paralysis of muscles or deformity. Skiagraphic examination is sometimes of value in showing deformity of the trachea.

The family history is often of interest, but is not essential to the diagnosis of simple goitre. In women the history of the sexual organs in relation to the goitre should be ascertained.

Simple hyperemia of the thyroid is differentiated by the small size and symmetry of the swelling, the soft consistency, the history of one or more of the causes of that condition, and the course. It is important to remember that such a goitre is occasionally followed by some other form, especially Graves' disease. The search for thrills and murmurs, and for the other signs of Graves' disease, is imperative in all these cases.

Parenchymatous or follicular goitre is recognized by its greater hardness in some cases, but there are many mild conditions in which a differential diagnosis between this and the preceding form is impossible. The detection of nodular hard areas should raise the suspicion of parenchymatous goitre or fetal adenoma. Colloid goitres are usually large, often asymmetrical, of softer, somewhat doughy consistency. They occur in rather older patients than the varieties just described. Vascular goitre and the rare aneurismal goitre are generally easy to recognize. In the former, Graves' disease must be excluded. Fibrous goitre is distinguished by its hard nodules, strands, or masses. It is especially frequent in long-standing cases, and especially in the irregular or grotesque forms seen in severe endemic goitre, and is then only part of the process. Mixed goitres are recognized by their different consistency in various parts. Hard and rapidly growing areas, especially if nodular, are suggestive of malignant disease.

The existence of cysts in goitres is of great therapeutic interest. Large cysts with fluctuation are easy to recognize, especially if superficial. Small ones are impossible to detect by ordinary methods, and even cysts holding 10 or 15 cc., if in the midst of a large parenchymatous goitre, may be overlooked. In all doubtful cases a careful exploration should be made with an aspirating syringe, under aseptic precautions, using a sharp needle, and avoiding unnecessary traumatism. The existence of a cyst, or of multiple cysts, can be made out by careful exploration and examination of the fluid. A fluid resembling pure blood is important to examine microscopically. Cholesterin crystals, an excess of leukocytes, or large granular cells indicate cysts in such cases.

Aberrant goitres in the neck are often impossible to distinguish from other tumors or cysts. Extirpation is usually indicated, and the positive diagnosis can then be made. Iodine treatment is sometimes useful, but should not be used for indefinite periods as a diagnostic agent.

Retrosternal and retroclavicular goitres should be suspected when there are attacks of suffocation, especially on lying down or while asleep, with physical signs of tumor in the upper part of the thorax, or when there are signs of thoracic tumor without a thyroid gland in the neck. Sometimes the relation of the growth to the thyroid above the clavicles can be shown by swallowing movements. The *x*-ray examination may be of service. Tumor of the root of the tongue should always excite suspicion of lingual goitre.

Prognosis.—Simple goitre is usually a chronic disease. Acute goitres, or small parenchymatous chronic goitres that have not lasted long enough to undergo degeneration, may recover under medicinal treatment or spontaneously, especially by leaving the locality in which the goitre was acquired, by changing the drinking water, or having it boiled.

In the case of long-standing goitres the course depends upon the position of the tumor, the presence or absence of pressure upon the trachea, œsophagus, nerves, and veins, and the occurrence of malignant change or inflammation. Position, and not size, is the important factor in such cases. Increase of pressure sometimes occurs from sudden hemorrhage into the tumor or from sudden increase of the rate of growth, and may radically change the prognosis. Sudden death can occur in such cases from tracheal stenosis or heart disease, less frequently from complications in the bronchi or lungs, from spasm or œdema of the glottis, or apoplexy. Tracheal stenosis from pressure on the tumor by the muscles of the neck is a possible cause of death.

Treatment.—Prophylaxis.—The most important task in connection with goitre is prevention. In countries with endemic foci this is an economic problem not less important than the prevention of the common infectious diseases. Besides sanitation in its broadest sense, the prevention of goitre requires the elimination of special factors, if they can be found, such as water supplies, that play a part. If possible, persons in predisposed families should leave goitre districts and live in healthier localities. Drinking water should be boiled. The suggestion that iodine be taken with food (Wagner-Jauregg, and others) deserves consideration, but if used, sea-salt is perhaps the best medium. Tight collars and occupations that induce congestion of the head should be avoided. Many of the assisting causes can, of course, not be wholly avoided. Treatment of the goitre is therefore necessary, because, in addition to the general indication, or the removal of deformity, there may be serious mechanical consequences or still more serious results of altered function of the diseased gland. Even a small goitre, diffuse or nodular, should be looked upon as serious, because it may cause pressure on important organs, or may lead to extensive atrophy from pressure in the healthy part of the thyroid, with functional disturbances.

The medicinal treatment of goitre is included in the one word iodine. This has been used for centuries, in the form of burnt sponge, and as the

element of various salts since 1820, but we are only now beginning to understand the most efficient methods and the rationale of the treatment.

It has long been known that small, or recent goitres, those in young people, the parenchymatous forms rather than the more atypical goitres, are more amenable to treatment. A. Kocher has pointed out some interesting relations between iodine and goitre. In healthy persons ingested iodine is excreted almost completely in the first twelve hours. In cases of diffuse hyperplastic or parenchymatous goitres there is increased excretion of iodine; at the same time the goitres diminish in size. Nodular goitres without degeneration act in the same way. Degenerated nodular goitres and mixed goitres do not as quickly subside, if at all, but the iodine excretion goes on as in healthy people. Colloid goitres do not become smaller, but the excretion is increased. Under long-continued treatment the colloid undergoes changes, and late improvement may occur. The goitres that diminish under iodine contain little iodine and conversely.

From all that we know at present, it would seem that T. Kocher is warranted in calling iodine a thyroid tonic. It stimulates the morbid gland to healthy action, provided the condition is one of altered function and retention of secretions. It cannot be said to remove the cause of the disease directly, so that its specific character is peculiar.

So potent a drug is, of course, not free from danger. Under the name "iodism" a condition has long been known in goitre regions, occurring in certain people treated for goitre with iodine preparations. This is altogether different from the irritation of the mucous membranes seen in certain susceptible people under treatment with iodine or iodides. It is recognized now, as was suspected by Lebert long ago, as an intoxication by thyroid products, a thyroidism or artificial Graves' disease. Nervous excitement, loss of sleep, tremor, circulatory disturbances, with warm skin, sweating, frequent pulse, palpitation, vasomotor disturbances, asthmatic attacks, sometimes vomiting and diarrhœa—occur in varying degrees of severity. Emaciation follows if the condition continues, and a severe and fatal marasmus, such as ended the life of the botanist de Candolle, as described by Lebert. The condition sometimes comes on very quickly, without disappearance of the goitre. It is especially likely to occur if iodine is used in excess, and the latter depends upon the relation between ingestion and excretion. Since rapid subsidence of a goitre is rarely necessary, and since we have no simple method of determining the rate of excretion of iodine, it is best to give the drug in small doses, at intervals.

In certain goitres, as mentioned above, recovery is easily brought about. With small, recent, congestive or hyperplastic goitres in young people a few applications of a solution or ointment of iodine over the gland often have an apparently miraculous effect. In larger or older goitres external treatment is often ineffective, the solutions are irritating, and the ointment disagreeable.

Solutions taken internally should be used, and 2 decigrams (3 gr.) of iodine daily (4 cc. or 1 fluidram of liquor iodi compositus) will produce

a notable effect in favorable cases. With such a dose, three-fourths the amount will be excreted by the urine in forty-eight hours (A. Kocher) so that it is safer if used every other day. Smaller doses may be given daily, such as ten minims of Lugol's solution, corresponding to 0.1 gm. (1.5 gr.) of iodine three times a day, but the patient must be carefully watched. If the goitre goes down quickly, in one to two weeks, as it does in favorable cases, the treatment can be stopped. If not, interrupted administration is preferable, giving 0.1 to 0.2 gm. every day or other day for a week or two; stopping two weeks, and repeating as necessary. Even in colloid goitres the treatment is sometimes effective after a long time, even up to two or three months. Sometimes a goitre will promptly subside, but only partially, and it can then be discovered that the condition is complicated, usually by a cyst, sometimes by a solid growth. Cysts, fibroid masses, calcified areas, and old goitres generally are not influenced by iodine, and it should not be given for them.

Iodine preparations have been extensively used by *injection* into goitres. The method is very dangerous, and should never be used until simpler methods have been tried. T. Kocher uses injections in the treatment of those goitres in which iodine may not reach the gland through the circulation, especially large colloid or nodular goitres. The tincture of iodine should not be used. Iodoform ether and iodoform oil are safer, still better 2 per cent. solution of potassium iodide, injected slowly (1 to 5 cc.). A different indication has been met by the injection of irritating solutions, iodine and others, into cystic goitres. This is less certain and more dangerous than extirpation. There is no advantage in using organic or other complex preparations of iodine rather than Lugol's solution or a simple tincture.

Thyroid, which has been used extensively since it was first advocated by Reinhold, often gives good results, but until there is some way of standardizing the preparations, thyroid must be looked upon as less exact than iodine and not essentially different. Iodothyrin has been extensively used also, but it is not to be preferred to inorganic iodine.

Goitres amenable to iodine subside quickly under *x*-ray treatment. In general there is no advantage in such treatment, although further observation may reveal special indications that can be met in that way.

In cases of goitre with severe symptoms it is proper to carry out more intensive iodine treatment under careful supervision, but only if the goitre is one that seems favorable for such treatment. In many of these, and in all cases not amenable to medicinal treatment, surgical intervention is necessary. In the hands of Kocher, Bruns, Kroenlein, Halsted, C. H. Mayo, and others the surgical treatment of goitre of all kinds has become a safe operation. The details belong to surgical works.

McCarrison's recommendation[1] of thymol, 10 grains twice a day, avoiding solvents (alcohol, oils) based upon his experiments in causation, is worth following.

[1] *Lancet*, January 25, 1913.

EXOPHTHALMIC GOITRE.[1]

Synonyms.—Basedow's disease; Graves' disease; goître exophthalmique, cachexie exophthalmique (French); Basedow'sche Krankheit, Glotzaugenkrankheit (German); morbo di Flajani, struma *seu* gozzo esoftalmico (Italian); bocio exoftalmico (Spanish).

Definition.—Exophthalmic goitre is characterized by an alteration of the thyroid gland, which is usually enlarged, and by tachycardia, palpitation of the heart, protrusion of the eyeballs, or tremor, or any combination of these, with some or many other symptoms on the part of various organs.

Etiology.—*Frequency.*—The belief in the general rarity of exophthalmic goitre is rapidly giving way. As Charcot said, we see what we know, and it is remarkable how even at this day well-marked cases are occasionally overlooked. Paessler, in Jena, saw 58 cases out of 2800 patients. The writer had 52 typical cases out of 5000 medical cases.

Sex.—Women are much more subject to exophthalmic goitre than men. Eight to one is probably the usual proportion in large series of cases, although Buschan, in 980 cases, found it 4.6 to 1. In Murray's 180 cases there were only 10 men.

Age.—Most cases occur between the ages of sixteen and forty. Cases in childhood are rare, but have been observed from birth on. After fifty the incidence in general is rare, and men then are relatively more often affected (1 to 3, Buschan).

Marriage and occupation seem to be unimportant in the etiology.

The family history is unimportant in most cases. In goitrous regions goitres are often to be found among mothers and sisters of patients with Graves' disease; occasionally an immediate relative, as mother, sister, or brother has Graves' disease. Rarely, a stronger family disposition is encountered, as in the experience of Oesterreicher: eight out of ten children of a hysterical woman had Graves' disease, and one daughter had three children with the same affection. In another instance, grandmother, father, two paternal aunts, and brother and sister were affected. Moebius looks upon the occurrence of simple goitre, often unnoticed, among the relatives of patients, as suggesting a congenital alteration of the thyroid, that can be converted into exophthalmic goitre by the influence of infection (typhoid fever, syphilis). Obesity and neuroses are more frequent among the relatives of patients with exophthalmic goitre.

The relations of locality and climate are obscure. The incidence of exophthalmic goitre seems to vary in different parts of the world, being higher in England and on sea coasts than in some continental localities, but it is very high in the interior of North America. It is sometimes said that endemic goitre districts are relatively free from exophthalmic goitre,

[1] The name preferred in most classifications. For the early history and bibliography of exophthalmic goitre, consult: G. Buschan, *Die Basedow'sche Krankheit*, Leipzig u. Wien, 1894; P. J. Moebius, *Die Basedow'sche Krankheit*, 2 ed., Wien, 1906; H. Sattler, *Die Basedow'sche Krankheit*, Leipzig, 1909–10; G. Dock, *Jour. Amer. Med. Assoc.*, 1908, October 3, p. 1121.

but this is not true of Switzerland and France or of the region of the Great Lakes of North America.

Among the traditional causes of exophthalmic goitre *fright* has always occupied a prominent place. This view is doubtless assisted by the resemblance of a typical Graves' facies to the picture of fright. Actual fright, sudden or prolonged, must be a rare cause, but various emotional shocks seem to have close relations in many cases. Careful inquiry often discloses the probability of the disease being in existence in a mild or latent form before the shock. Thus, one woman, aged twenty-five years, had palpitation of the heart for some months, following influenza. She was then frightened by thinking her child had drunk carbolic acid, had so rapid a heart beat that she was supposed to be dying, and was confined to bed for three months with tachycardia, nervousness, and weakness.

A long-continued history of *worry*, with or without adequate cause, is often given. Hard, physical labor, with worry, or with loss of sleep and insufficient food, can sometimes be traced. In some cases prolonged dancing has been given as a cause. Buschan especially has given many proofs of the neuropathic origin and relations of exophthalmic goitre, but probably this has been exaggerated as a causal factor. Many patients give a history of "nervousness," or "nervous prostration," long before the other symptoms. Many are neurotic looking. But many others are free from such phenomena until the onset of the exophthalmic goitre. There are comparatively few who have hysterical stigmata or histories, nor are they easily influenced by suggestion, if we except the frequent response to treatment of any kind for the Basedow symptoms. Even then they are not equally suggestible in regard to all symptoms—*e. g.*, their constipation is often refractory to psychic treatment. The writer has been especially impressed with the above view because his goitre patients of all kinds live in a region where neuroses are common, but the neurotic subjects and families are much more likely to have gastric or sexual neuroses than exophthalmic goitre. Many of them also have small, simple goitres, but do not show Basedow's signs to a notable degree after taking iodine or thyroid extract.

"Colds," sore throat, tonsillitis, or other acute infections often precede the symptoms of exophthalmic goitre. In some cases a swelling of the thyroid during or after the acute disease suggests acute thyroiditis. In patients with simple goitre an acute inflammation sometimes seems to form the connecting link with Graves' disease. Thus, a woman, aged thirty-three years, was treated for a parenchymatous goitre, which under small doses of iodine became so small as to be hardly visible. There were no signs of Graves' disease at any time during observation for three months, and medication was stopped. An operation for displaced uterus was undergone, with no untoward symptoms. Five months after treatment was stopped there was an acute sore throat. In about two weeks the thyroid became larger and painful. Without consulting any one the patient had a friend massage the gland. In a few days she had palpitation, thrill over the thyroid, weakness of the legs, and a belief in a change in her condition, followed in a few weeks more by many marked symptoms. The thyroid was only slightly enlarged, but was the seat

of unusual thrill, murmur, and visible pulsations. There was Stellwag's sign, but no Graefe or Moebius sign. Engel-Reimers has called attention to the frequency of secondary syphilis in the early history of exophthalmic goitre in young married women. Other diseases that occur in a similar connection are rheumatic fever, typhoid fever, scarlet fever, measles, whooping cough, mumps, and malaria. Some of the writer's patients had a striking history of exacerbations of Graves' disease with severe tonsillitis, a coincidence that has been observed by others.

W. B. Stanton[1] has called attention to the frequency of Basedow's symptoms in tuberculous subjects, and in the thyroid glands of fatal cases of tuberculosis he found tubercles in a notable proportion of cases. In the thesis of Dumas[2] a number of cases are cited. Hufnagel, in 1246 children, found 6 with apical tuberculosis and Basedow's disease. In one case an attack of measles was followed by exacerbation of both tuberculosis and exophthalmic goitre.

The importance of chlorosis as a cause is not mentioned now as often as it was in the early days. In many cases the condition is the pseudo-chlorosis of exophthalmic goitre.

The relation of pregnancy to exophthalmic goitre is variable. Sometimes Graves' disease begins in pregnancy or in the puerperal period, or later. On the other hand, many patients with the disease improve during pregnancy and do not relapse afterward. The writer's experience leads him to think, with Charcot, that if the condition of the patient is not too serious, pregnancy is of advantage to the patient with exophthalmic goitre. Diseases of the pelvic organs in women have no definite bearing on the occurrence of exophthalmic goitre. Undeveloped sexual organs and menstrual disorders do not seem especially concerned. Hoennicke believes in a relationship between osteomalacia and Basedow's disease, which suggests an ovarian source, but this is certainly rare.

Nasal and pharyngeal abnormalities have been supposed to be responsible for some cases of exophthalmic goitre, but the relations are far from clear. The same may be said of floating kidney.

Many writers have called attention to the frequency of gastro-intestinal disturbances. Enteroptosis seems less common in patients with exophthalmic goitre than in others.

From the action of iodine in bringing out latent symptoms in patients with exophthalmic goitre, not only iodine, but other chemical substances have been supposed to be occasional causes of the disease, but nothing positive is known about them.

From the study of the etiological factors it seems certain that these vary much in mode of action. Some, such as sex, must be purely predisposing. Others, like shocks and worry, may act by rousing a latent disease (possibly by exciting it without latency), while others, such as infection, seem to be capable of bringing it on more directly. It seems most probable the causes are many and various. Perhaps the mechanism is not always the same. Sometimes there may be a nervous stimulation of the thyroid gland, sometimes a stimulation by toxic, infectious, or

[1] *Amer. Med.*, 1905, x, 605.
[2] *Goitre exophthalmique d'origine tuberculeuse*, Lyons, 1907.

metabolic substances. If, in addition to these variations of the process in the thyroid, we include reflex or chemical irritation of other glands, ductless, sexual, and others, and the varying influence of excretory poisons, we have no difficulty in explaining, theoretically, all the varieties of the disease. However, the diagnostic and therapeutic relations are much more deserving of attention than theories that cannot at present be put to the test.

Pathology.—All discussions begin now with the theory of Moebius, announced in 1886. According to this, exophthalmic goitre is an intoxication from morbid function of the thyroid gland. Moebius was not sure, nor are we now, whether the thyroid disease is primary or secondary. He thought the altered function peculiar, but admitted its occurrence in all kinds of goitres, or even in persons without previous goitres. One of the strongest supports of the theory is the contrast presented to exophthalmic goitre by myxœdema, a disease due to thyroid deficiency. In many cases the contrast is complete; in some others the two conditions seem mixed. This does not necessarily weaken the theory, for we may admit that a disease causing deficiency may also set up irritative processes that lead to hyperactivity. Another support is given the theory by the results of grafting or of feeding, or by the administration of thyroid preparations as medicines. They present some of the most frequent symptoms of Graves' disease, but in the majority of cases there is no exophthalmos. This symptom, however, was present in a case reported by von Notthafft[1] in 1898. A man, aged forty-three years, without neurotic antecedents, took about 1000 five-grain thyroid tablets for obesity in six weeks. By the third week he had thyroid enlargement of about 3 cm. Dyspnœa, palpitation of the heart with bounding carotid arteries, depression, and mental excitement with insomnia followed. A warm skin, moderate exophthalmos, and tremor were present, but the thyroid, although distinctly enlarged, was free from thrill and murmur. The pulse was 120, the apex of the heart forcible and displaced outward. Stellwag's and Graefe's signs were present. There was glycosuria. Recovery followed rather rapidly when the medication was discontinued, but the exophthalmos and lid signs persisted for six months. Exophthalmos has also been observed in experiments with thyroid juice (Kraus and Friedenthal) and thyroidin (Hoennicke).

There is a close resemblance in the metabolic changes following excessive ingestion of thyroid preparations and those of exophthalmic goitre. Mathes had a patient successfully operated upon. Afterward, on feeding him with his own dried thyroid, there was a characteristic increase of nitrogenous metabolism with return of the symptoms. Reid Hunt's experiments seem to show an increase of thyroid secretion in the blood in exophthalmic goitre. He suggests that not only is there excessive secretion, but also diminished power in the blood to destroy it.

Important confirmation to this theory has been given by the results of surgical operations involving removal of part of the gland. This has been done on a scale so large as to exclude coincidence and

[1] *Centralbl. f. inn. Med.*, 1898, No. 1[illegible]

suggestion. That many experiments on animals have been negative is not remarkable, if we accept the need of predisposition, not only on the part of the thyroid, but also on that of all the other glands of internal secretion and also the nervous system. Oswald, Minnich and others have suggested "dysthyroidization," or intoxication by an altered secretion. Until we know more about the normal secretion and its modes of action the suggestion has no very great working value. The fact that thyroid administration is sometimes followed by improvement of exophthalmic goitre is not against the Moebius theory. On the one hand, the action may be only "post hoc," on the other the action of iodine bodies may be beneficial in a symptomatic or a partial way.

Elements that seem beyond question are the increased parenchymatous tissue and increased vascular activity of the thyroid gland, greater reactivity of the nervous system, especially the vegetative system, and certain alterations, degenerative often, of other glands with internal secretions.

Morbid Anatomy.—*The Thyroid Gland.*—A belief in the existence of a distinct and to a certain extent specific alteration was first advanced by W. S. Greenfield (1893), and has been confirmed by many others, especially Renaut, Waehner, Edmunds, Farner, L. R. Mueller, Hirschlaff, Dinkler, Haemig, Ehrich, Lubarsch, Hansemann,[1] W. G. MacCallum,[2] Lewis,[3] Ewing,[4] Wilson,[5] and MacCarty.[6] A. Kocher, who was at first opposed to it, now adds the authority of the Bern clinic to the prevailing view.[7] The essential changes are increase of parenchyma and stroma with disappearance of colloid. The hyperplasia, however, is not normal. The epithelial cells are increased numerically, but grow in an atypical way. There is a general relation between the anatomical process and the severity and stages of the clinical course, but this is not equally clear in all cases. MacCallum's description is so excellent that it is given very fully in the following: "The thyroid is enlarged, although, as a rule, not to a great size; in some cases it is not larger than the normal, or it may be actually decreased in size. At operation the superficial veins are found to be very large and easily torn and are distended with blood, so that the gland has a very congested appearance. This is not striking in the excised portion, since the vessels collapse, and on section the interior of the gland tissue is rather pale. Usually the tissue is hard and rather rigid than elastic. Its normal amber red translucence gives way to a grayish opacity, and the fresh cut surface, instead of being glairy or gelatinous in appearance, tends to be rather dry and granular. This varies with the amount of colloid material in the alveoli, and in many advanced cases the cut surface may be still moist and give off a little glutinous material. The surface of the gland is usually somewhat nodular and rough, and this is seen to be true

[1] *Berl. klin. Woch.*, October 30, 1905, Festnummer, p. 65.
[2] *The Johns Hopkins Hospital Bulletin*, 1905, xvi, No. 173.
[3] *Surgery, Gynecology, and Obstetrics*, 1906, iii, 476.
[4] *Trans. Assoc. Amer. Phys.*, 1906, xxi, 567.
[5] *Amer. Jour. Med. Sci.*, December, 1908, p. 851; *Trans. Assoc. Amer. Phys.*, 1913, xxviii, 576.
[6] Collected Papers by the Staff of St. Mary's Hospital, Mayo Clinic, 1912–1913.
[7] *Virchows Archiv f. path Anat. etc.*, 1912, Band ccviii, pp. 86, 161.

also of the cut surface, in which it is found that fine strands of fibrous tissue traverse the glandular substance, separating it into lobules.

"Usually the change is diffuse throughout the whole gland, but sometimes one lobe may be much larger than the other, and in some cases the alterations described are present only in small patches here and there throughout a gland which otherwise seems normal. These foci are easily distinguished by their fine grain and by their opacity from the adjacent colloid holding tissue.

"Microscopically there is found the change which appears in experimental compensatory hypertrophy (such as Horsley and Halsted found in partial thyroidectomy). Strands of fibrous tissue run in every direction like scars through the gland and separate the tissue into lobular masses, and in these lobules the alveoli are often separated by a fibrous tissue stroma much more abundant than in the normal gland. The alveoli are no longer rounded, full of colloid, and lined with low, cubical epithelium, but are extremely irregular in size and in form. As a rule, most of them are smaller than normal, while in the central part of each small lobule there are larger alveoli of very irregular outline, sending out diverticuli in every direction and encroached on by epithelial projections which extend into their lumen. With some special methods of staining the connective tissue it may often be made clear that such a small lobule is probably a sort of colony in which the smaller peripheral alveoli are derived from the more centrally placed, or are actually merely sections of the diverticula of the central ramifying alveolus. This alternation of large, irregular alveoli with small ones ranged around them is very characteristic, and evidently results, in part at least, from the separation of portions of the central cavity in the form of new alveoli.

"The epithelium becomes columnar not only in the large alveoli, but in the small ones as well, and thus occupies so much space that there is but little lumen left. Indeed, the areas occupied by the small alveoli may appear almost solid, so small are their cavities and so scant the colloid. In most instances the epithelium is very regular in its form throughout, and the details of its structure can be made out very clearly. The cells are plump, with a finely granular protoplasm and a sharp outline. The free surface is very sharply marked and is sometimes slightly dome-shaped. The nucleus may lie near the base or near the free end of the cell. Mitotic figures are frequently to be found. Occasionally some of the cells appear narrow and shrunken and biconcave in form, with very deeply stained nucleus and dark red protoplasm.

"In extreme cases peculiar alterations of the epithelial cells are sometimes found. In several instances we have observed areas in which the epithelium was enormously swollen, so as to practically obliterate the lumen of the alveolus. These large, irregular cells no longer preserve the columnar form, but are shapeless masses of finely granular protoplasm which takes an intense pink stain with eosin and in which the nuclei are also irregular in form and size and stain very deeply, almost black, with hematoxylin. Usually one or two alveoli only show such a change in their epithelium, or there may be only a few cells of this form

intercalated among others of the usual type in the alveolar wall, but sometimes over considerable areas all the alveoli are packed with such cells. Their significance is far from clear. Much more frequently there are found cells among the ordinary epithelial cells of the alveolar wall which are greatly enlarged, but the protoplasm of which retains the characters seen in the rest of the cells and contains only a scant basophilic granulation. The nuclei of such cells are usually much enlarged and vesicular, with scattered chromatin granules.

"The colloid varies greatly in different cases, but it seems that in most of the more severe cases it is markedly diminished in amount and altered in quality, the normal hyaline material being replaced by a very palely staining substance or by a ragged, shreddy, granular, or vacuolated mass which has no longer the refractive qualities of the normal colloid. There are some cases, however, in which there is a great deal of fairly normal looking colloid, and this is especially true of those instances in which the hypertrophy of the epithelium is relatively slight; cases, that is, in which the process is apparently advanced, at least so far as the thyroid is concerned. On the other hand, when the colloid is greatly diminished one rarely fails to find severe symptoms, and when the symptoms are very indefinite or in part absent it is usual to find a good deal of colloid.

"The most interesting cases are those in which intense symptoms exist, but in which at the same time the alveoli contain a large amount of colloid. Although in some cases one may explain the existence of such large alveoli full of colloid, on the idea that the exophthalmic symptoms are associated with changes which have appeared in a gland already the seat of alterations such as are seen in a colloid goitre, still there remain many in which there is no evidence of such a previous goitrous change. From this it appears that the presence of quite abundant colloid is not inconsistent with the development of intense symptoms, although in most cases in which the symptoms are intense the colloid tends to disappear with the advance in the alterations in the gland. One can distinguish, however, different types of change in the thyroid in different cases, for while in one group the alveoli are not larger than normal, show elevation and folding of the epithelium, and are full of colloid, another group with quite as intense symptoms will present thyroid tissue composed of very large alveoli full of colloid in which, nevertheless, the folding of the epithelial layer is most complicated. A third group comprises cases usually milder in their course in which the alveoli are large and full of colloid, but in which the alveolar epithelium is almost flat, except in certain foci or in portions of some of the alveolar walls, where it becomes cylindrical and thrown up into folds. Several cases in which extirpation of the thyroid was carried out with good results for the relief of indefinite symptoms, such as the combination of goitre with tremor only or with moderate tachycardia only, showed in the thyroid abundant colloid in large alveoli which are hardly at all irregular, but nevertheless in places show areas of epithelium which has become high and cylindrical and which is beginning to project prominently into the alveolar lumen.

"In a few cases in which the symptoms were reduced to nervousness

or slight tremor with goitre, the excised tissue shows the normal structure or that of a circumscribed adenoma.

"The focal nature of the alterations in the thyroid is especially interesting, and may be recognized in some cases in the fresh cut surface of the gland by the opacity and granular surface of the altered areas which contrast with the surrounding tissue. Apparently this, too, represents a stage in the development of the lesion, and in most of the six cases which show it the symptoms had existed only a short time before the operation. Microscopically the altered areas are quite sharply demarcated from the rest and may involve a great number of alveoli, or be limited to very small foci, including only a few alveoli here and there.

"In sixteen cases there were found, on cutting through the thyroid, rounded, circumscribed nodules which projected above the general level and differed in consistency and general appearance from the rest of the gland. These are the adenomatous nodules which constitute a considerable proportion of ordinary goitre, and hence they are by no means peculiar nor characteristic of the changes in exophthalmic goitre. They are most commonly finely granular and opaque, occasionally flecked with yellow patches of necrosis or with hemorrhages, and on section they are seen to be composed of small, round alveoli lying quite separate from one another in an abundant loose stroma and lined with cubical epithelium. In only a few cases did the alveoli which make up such embedded nodules show the folding and other hypertrophic changes which characterize the tissue round about, but in one case in which exophthalmic symptoms were well marked these changes were limited to the tissue forming such a circumscribed nodule. In another case the hypertrophied tissue was found to form the thick lining of a cyst.

"In six cases it was possible to study the thyroid at different stages in the progress of the disease, either in tissue removed at two different operations or at autopsy in patients who died some time after the operation. No very constant results were obtained. In four of the cases, in which the intervals between the times of obtaining the two specimens were seven months, eighteen months, forty-five days, and seventy-nine days, the tissues were practically identical in the two portions examined. In the fifth case, after a lapse of nine months, the tissue from the second operation showed that the epithelial cells had become greatly increased in height and the colloid rather more abundant. In the case in which the longest interval elapsed between the operations, two years and six months, the alveoli had changed from small, compact, almost solid masses of epithelium, with inconspicuous lumen and no colloid, to large ramifying spaces full of ragged colloid and lined with very high cylindrical epithelium."

Among the other anatomical changes that are seen in exophthalmic goitre the most striking only need be mentioned.

Lymphatic System.—In the Graves' thyroid there is a frequent appearance of lymphoid tissue in unusual quantities. It occurs in small or large masses of cells with germinal centres, scattered around in various parts of the gland. The lymphatic and hemolymph glands in the neck are often found enlarged, especially at operation. In the lymphatic ves-

sels near the thyroid, colloid material has often been described, but it is doubtful whether it is always true colloid. Besides the glands near the thyroid, the bronchial and mesenteric glands, as well as those in all other parts of the body, may be large. The tonsils are often large.

The *spleen* is often enlarged, but usually shows no characteristic histological change. It may be the seat of various accidental degenerations.

The *thymus* is very often enlarged, and many recent writers give it a more or less important place in the pathology of exophthalmic goitre. A relation to the blood changes and some of the heart symptoms is probable.[1]

Parathyroid Glands.—The investigations of MacCallum prove that the part played by these bodies in exophthalmic goitre is neither important nor specific.

Sympathetic System.—Much attention has been given to the sympathetic ganglia and nerves, and many cases have been described in which there was degeneration, atrophy, pigmentation, or calcification. In other cases no alterations have been found. Any that do occur are likely to be secondary.

Central Nervous System.—Atrophy, degeneration, and minute hemorrhages in various parts of the central nervous system have been described, but none of them are constant, and none of them can be brought into relation with more than a few of the numerous symptoms of the disease.

Hypophysis.—The importance of changes in the hypophysis seems to have been exaggerated. MacCallum, like some others, found no evidences of disease in one case.

Muscles.—So striking is the muscular weakness in exophthalmic goitre that it is remarkable so little has been done in the histological examination of those organs. M. Askanazy[2] has described a fatty degeneration and atrophy of the muscle fibres, affecting especially the muscles of the thorax, abdomen and pelvis, eyes, and tongue, which he considers toxic in origin.

Other changes in organs are inconstant or secondary, so far as we can see at present. The chief constant lesions are those in the thyroid, thymus, and lymphatic glands.

Morbid Chemistry of the Thyroid Gland in Exophthalmic Goitre.—*Iodine.*—All who have investigated the thyroid gland chemically in exophthalmic goitre agree that the iodine is generally absolutely less than normal. Sometimes the reduction is so great that the gland is said to be iodine-free. In other cases it may be normal (2 to 9 mg. per gland) or may be increased. Caro[3] found 10 mg. in a case in which iodine had not been taken medicinally, while Oswald[4] found 35 mg. Two facts must be borne in mind in this connection: (1) The iodine depends on the colloid, in general, and a Basedow goitre may contain considerable colloid, as has been mentioned. (2) The richness in iodine is not the only factor as an evidence of function. More important is the question whether and how

[1] See H. Matti, *Deutsch. Zeitschr. f. Chir.*, 1912, Band cxvi, p. 425, for valuable discussion and bibliography.

[2] *Deut. Arch. f. klin. Med.*, 1898, Band lxi.

[3] *Berl. klin. Woch.*, 1907, p. 519.

[4] *Wien. klin. Woch.*, 1905, p. 649.

rapidly the secretion enters the circulation. In the iodine-poor secretion of a hyperplastic gland the circulation can freely carry away iodine; in the colloid areas it may remain fixed.

Symptoms.—The symptoms occur in great variety, and in many combinations and varying sequences. It seems better, therefore, to describe the individual symptoms first, and then to refer to the chief varieties of type. Any classification of the symptoms at present must be artificial, and the order is followed which has the advantages of custom.

The Thyroid Gland.—The proportion of cases in which Graves' disease occurs in subjects of old simple goitre varies in different localities. In such cases the size, shape, and consistency of the thyroid differ considerably from others. The gland may be of considerable size, and unsymmetrical; may be hard or soft, cystic, adenomatous or fibrous, to a greater or less extent. It is impossible to learn in all cases whether there was a goitre before other symptoms came on. Many people have goitres of considerable size without knowing it. Sometimes the characteristic or Basedowian goitre comes on rapidly, within a few weeks, days, or even hours. It may then remain stationary, or may vary from time to time. Sometimes the exacerbation coincides with menstruation or some other process; sometimes no explanation can be given.

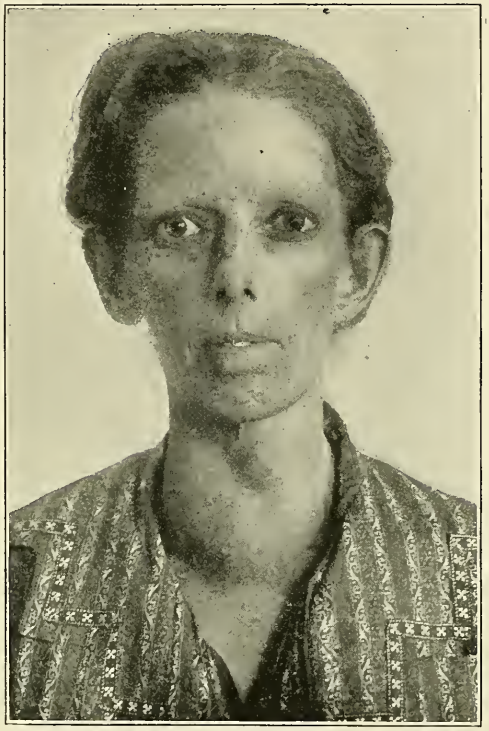
In some cases no enlargement can be made out by the most careful examination. From what we know of the pathological anatomy of the Basedowian thyroid, this is not remarkable. It is obvious there may be extensive alterations of the gland without enlargement, or even with a reduction of the size absolutely, or as compared with the average. Clinically such cases are rare, especially in the experience of those who take pains to make careful examinations, and when repeated examinations are made. For example, Murray, in 180 cases, found goitre absent only 8 times, and in 5 of them there was a history of goitre at some time. The writer has seen only one case (one examination) in which the gland was not distinctly enlarged. Kocher found the gland at operation always enlarged.

In general, the enlargement is not great. Murray makes a useful classification of size as follows: (1) Slight, when the gland can be distinctly felt, though not noticed by the patient; (2) moderate, when it can be seen and felt; (3) considerable, when it is obvious and disfiguring; (4) enormous. Most cases fall under the first two classes, about equally divided. Murray found one-sixth of considerable size, a larger proportion than many others have found. He also records a rare "enormous" goitre, in which the neck measured twenty-three inches. The enlargement had existed thirty-four years. Usually all the lobes are enlarged, including the pyramidal process if present. In many cases the enlargement of the lateral lobes is equal. In about as many the right lobe is larger, in a few the left. The surface is usually smooth in small goitres, uneven, nodular or granular, or very uneven in larger ones.

The consistency is rarely hard. More often it is firm elastic, or soft elastic, or soft. Sometimes it is very soft, almost like a varicocele. In many cases there is visible pulsation in the lateral lobes, sometimes transmitted from the carotids; sometimes the veins over the goitre show marked

pulsation, or the whole goitre pulsates. In other cases there is palpable pulsation only. In many cases there is a more or less distinct thrill over the whole of the enlarged lateral lobe, sometimes only over the larger one if they are uneven; sometimes only at the upper poles, rarely the lower.

Fig. 63



Exophthalmic goitre.

On auscultation there is usually a systolic murmur, sometimes a diastolic as well as systolic murmur, less frequently a continuous murmur, sometimes with systolic accentuation. It varies much in character from a soft blowing to a musical twang or squeak, called by Fuller the sleigh-runner murmur. According to P. Guttmann, who first called attention to the diagnostic importance of the murmur, the systolic part is arterial, due to hypertrophy of the left ventricle and the uneven dilatation of the arteries in the gland; the diastolic murmur is venous and anemic. The vascular phenomena may be present when the thyroid is apparently not enlarged. Murmurs may be absent for shorter or longer periods. They do not depend upon the propagation of heart murmurs.

In general the enlarged thyroid of Graves' disease is not painful or tender, but may be so in the beginning or during temporary increase of size. The goitre rarely causes pressure symptoms, but when the disease

is added to an old goitre there may be pressure on the trachea or nerves, and the symptoms vary according to the size of the goitre.

Circulatory Phenomena.—Patients rarely fail to notice changes in the rate and rhythm of the heart-beat, and in many cases palpitation or frequent pulse is mentioned as the earliest symptom. At first "palpitation" is noticed only after exertion or excitement, and is then important only when it is unusual for that patient. Sometimes it is associated with a feeling of suffocation, or swelling in the throat. It is suggestive when palpitation occurs in persons who have no discoverable cause. Much more constant and important, by the time patients come under observation, is frequent pulse, tachycardia,[1] which may exist without the patient knowing it. This varies from 90 to 120 or 140 to the minute, but at times may reach much higher rates—225 in one of the writer's patients—for many hours. In the rare cases without frequent pulse—60 to 80, as in two of the writer's (male) patients—it is possible the normal pulse was still lower. The tachycardia usually shows a close relation to changes in the severity of the disease. Even in fairly constant improvement the pulse is likely to be higher than would be expected from the age and condition of the patient.

The cardiovascular phenomena are universally admitted to be thyrogenic, but their exact origin is unknown. It is obviously not mechanical. Tachycardia can sometimes be brought out by ingestion of thyroid preparations, and Pfeiffer[2] saw frequent pulse in dogs after administration of human thyroid secretion, but Paessler and Schultze[3] had negative results. Such experiments obviously do not imitate the process in exophthalmic goitre, and until the mechanism of acceleration and depression of the heart and the qualities of thyroid secretions are better understood, speculation is not likely to add much to our knowledge.[4]

Postmortem the heart usually shows hypertrophy, especially of the left, sometimes the right (Fr. v. Müller), ventricle, with dilatation, and with relative insufficiency of the valves. Endocarditis, also arteriosclerosis, may be associated. The enlargement of the vessels in the thyroid does not show, as a rule, after death, but the thyroid arteries may be relatively more sclerotic or their walls may be attenuated.

Clinically the precordium is often prominent, especially when the disease begins in early life, and the whole heart area, or the whole anterior wall of the chest, may be made to heave with the forcible action of the heart. This may be perceptible through the clothing. On palpation it can be felt as an unusually violent impact—"pounding." Sometimes there is a systolic thrill or a diastolic shock. With this the apex beat may not be much displaced, or even if too far out, as the nipple-line, it may be in the fifth, or even the fourth interspace. The dulness is increased, especially to the left. On auscultation the sounds are usually loud, but the first sound is rarely clear. The sounds may be audible at a distance. Murmurs are common, especially at the apex, conducted

[1] Although not so accurate etymologically, "tachycardia" has the force of custom, and so is preferable to such terms as "pycnocardia," "polycardia," or "sychnosphyxia.

[2] *Wien. med. Woch.*, 1907, p. 1173.

[3] *Mitth. a. d. Grenzgeb.*, 1905, Band xiv, p. 330; *ibid.*, 1907, xvii, 655.

[4] See Minnich, *Das Kropfherz*, 1904; Discussion, *Congress f. inn. Med.*, 1906.

into the axilla; sometimes the same or a different murmur is audible over the base. Diastolic murmurs in the aortic area are sometimes present. Sometimes the murmurs are audible over the whole thorax or in the extremities. The causes of the murmurs are undoubtedly various. Probably muscular insufficiency is the chief factor, anemia a rare one. Valvular disease of endocarditic origin is sometimes associated, as it probably was in Parry's first patient, with a history of rheumatism. Reduplication of the sounds and gallop rhythm are sometimes present. Arhythmia will be mentioned below. Stenocardia, even typical angina pectoris, has been observed, but may be a complication.

The vascular anomalies are even more striking than the cardiac ones. The carotids alone may be involved, or those of the head (retinal arteries), or the head and body may be shaken at each heart beat, as in some cases of aortic regurgitation (sometimes called "Musset's sign," after Paul de Musset, who described it in the case of his brother, the poet). Capillary or even venous pulse (liver pulse, splenic pulse) may be present. Pulsation of the abdominal aorta is often annoying to patients with Graves' disease. The radial pulse is variable. Sometimes it is small and soft, sometimes small and hard, sometimes large. It is likely to be quick (celer) even when it feels hard, and this is borne out by sphygmographic tracings. The blood-pressure (systolic) is sometimes normal, sometimes low, but often high, even when the rate is not extremely high (P. Marie, Spiethoff, Donath, Morris and Edmunds, Dock[1]). The widespread view that the pressure is low is doubtless due to the quick pulse, which in turn depends upon a large pulse pressure. As T. C. Janeway points out, diastolic determinations are difficult to make, and all the factors are greatly modified by accidental causes, such as emotional excitement.

Arhythmia is not uncommon, but in most cases is merely an intermission of the radial pulse at longer or shorter intervals, from (ventricular, usually) extrasystole. Sometimes the extrasystole occurs at a certain phase of respiration. In other cases there are more marked arhythmias. There may be auriculoventricular arhythmia, with auricles and ventricles contracting simultaneously at certain periods and with visible, palpable (shock), and audible signs (extraordinarily loud tone) over the veins of the neck at those periods. Occasionally there is alternating pulse, with slight or marked disproportion of the beats. Sometimes the alternation is due to regular extrasystoles, and may then be mistaken for a dicrotic pulse and the pulse rate taken to be half what it really is. In other cases there is irregularity of force and rhythm, again leading to too low pulse count. The slight or regular arhythmias are of no special significance. The severe ones are usually of serious omen, as pointed out by von Graefe (1867), but some patients have been observed to have irregular pulse for many years without evidence of cardiac failure. In such cases tracings should be made, in order to enable us to learn whether there is any rule. Serious irregularity coming on early may be recovered from; later, with degeneration or insufficiency of the heart, it is less amenable to treatment.

[1] *Amer. Med.*, February 24, 1906, p. 271.

Erythema will be mentioned later. Hemorrhages sometimes occur from the nose, lungs, stomach, or skin. In some cases bedsores develop rapidly. Œdema will be mentioned below (skin). In rare cases gangrene, especially of the legs, has been observed.

Eyes.—Protrusion of the eyes was noted by Parry in his first case, and for a time formed one of the "symptomatic tripod" with goitre and palpitation of the heart. More extensive observation soon made it clear that exophthalmos, like the other signs, could be absent. It comes on comparatively late, and is present only in two-thirds to three-fourths of all cases. It varies much in degree, from a slight prominence of the eyeballs, that can only be recognized by one who carefully observed the eyes before, up to veritable goggle-eyes (Glotzaugen), or so that the bulbs actually slip past the eyelids. The degree bears no relation to the size of the goitre or the severity of the other symptoms. In many cases (one-seventh, Wilbrand and Saenger) the exophthalmos is unilateral, or is larger on one side. In the former case the other eye may become affected later. In some cases there is goitre on one side and exophthalmos on the other. The protrusion may come on in a few days or even minutes, but usually does so slowly, sometimes irregularly. In the early stages the swelling can be reduced by gentle pressure, but later this cannot be done. The cause and mechanism of the exophthalmos are still unknown. Postmortem an increase of orbital fat has often been noted, but the rapid protrusion in some cases proves that such a condition is not primary. Vascular congestion and œdema have been assumed. The latter is often present, with œdema in the folds between the lids and the edges of the orbit. Besides these causes, spasm of the orbital muscle of Müller, with or without weakness of the orbicularis, has been suggested. Experiments of MacCallum and Cornell[1] make it probable that this does play a part. Landström described a cylindrical band of smooth muscle fibres, rising from the orbital septum and inserted into the equator bulbi, leaving an opening for the levator palpebræ superioris. He thought this muscle could account for Moebius' sign, as well as the other ocular symptoms.[2] Hyperthyroidism, however it may act, seems to be the cause of the exophthalmos. Besides the cases of hyperthyroidism by treatment, experimental proof has been brought by Hoennicke,[3] who used normal thyroidin, Kraus and Friedenthal, and others. Its production takes time, and requires a predisposition as well as a certain relation between the bony orbit and the bulb. Fr. v. Müller points out the probability of some action of the thyroid upon the sympathetic. In two cases of unilateral exophthalmos there was goitre on the same side. In one of the two the goitre had been bilateral, and also the exophthalmos. After one side of the thyroid was removed, the exophthalmos disappeared on that side.

Exophthalmos is, of course, not peculiar to Graves' disease. Besides aneurisms, inflammation and tumors in the orbit, it is sometimes present

[1] *The Medical News*, October 14, 1904.

[2] *Ueber Morbus Basedowii*, 1907; also *Münch. med. Woch.*, March 31, 1908, p. 689. Troell, *Mitth. a. d. Grenzgeb.*, 1914, Band xxvii, p. 418, gives the whole matter destructive criticism.

[3] *Verhandlungen des Congresses f. inn. Med.*, 1906.

in cases of atheroma with dilatation of the arteries and in chronic cyanosis of the head. Marine saw it in a patient with gout and aneurism of the basilar arteries, with dilatation of the cerebral vessels in all parts. Fr. v. Müller points to its occurrence in some cases of lead poisoning as a toxic vasomotor condition.

Exophthalmos is rarely an early sign of Graves' disease. From the beginning numerous observers mentioned a peculiar lustrous appearance, or a staring of the eyes. The staring, with a diminished frequency of reflex winking, is now known by the name of Stellwag's sign. Dalrymple, according to W. W. Cooper (1849), explained the cause of the appearance, as we do now, to spasm of the levator palpebræ superioris, but Cooper thought the spasm was not peculiar to the disease, and it remained for Stellwag (1869) to show not only its mechanism, but its clinical value. The appearance is due to an exaggeration of that seen when the gaze is fixed, especially as in fright, showing sclera above the cornea, and giving the appearance of a glass eye. It occurs early, is rarely absent, varies from day to day in its degree, and sometimes is more distinct on one side. Stellwag's sign is not peculiar to exophthalmic goitre. Besides fright it occurs in maniacal conditions, in hysteria, tabes, and pregnancy. It is related to the lessened frequency and completeness of winking, although the two symptoms do not always coincide. Many patients with Graves' disease wink as often as normal persons. Its explanation is generally found in a higher excitation of the nerves.

Graefe's sign consists in the loss of agreement between the motion of the lids and the raising or lowering of the plane of vision. It is seen especially when the patient looks from above downward. The upper lid then falls more slowly or even jerks back. The sign cannot be seen so well in the lower lid, although if the patient looks up, the jerking of the upper lid can also be seen, sometimes, in that motion. Graefe's sign is not always present, nor at all times in cases where it does occur. Authors differ much in their observations. The writer found it in about half the cases, as did Lewin (55.5 per cent.), varying much at different times. Griffith found it in 13, Paessler in 14, and West in 17.6 per cent. of cases only. It is generally present on both sides. Graefe's sign is sometimes present in healthy people; Raymond found it in Thomsen's disease. It is sometimes present with ptosis. Wilbrand and Saenger,[1] who discuss the matter fully, give five theories of the cause of the symptom, viz., sympathetic; central; action of orbital vessels upon the levator; insufficiency of the orbicularis; increase of the forces that cause elevation. It is important to note that other evidences of sympathetic irritation (dilatation of pupils) are rarely present, and the authors cited believe there is either muscular irritation or mechanical relations with the exophthalmos. Ptosis sometimes occurs, but usually without evidence of sympathetic disease.

Another sign connected with the eyes is that described by Moebius, and called after him by Charcot. In this, if the patient fixes his eyes on the tip of his nose, or better, an object on the level of his eyes and near

[1] *Die Neurologie des Auges*, Band i, p. 45.

them, one eye turns out. There is no diplopia with this. Some patients complain of fatigue in the eyes at the time, others do not. It does not depend upon exophthalmos, but may be favored by that. The sign is of relative value only. It occurs in many myasthenic conditions.

As to other symptoms on the part of the eyes and their appendages, severe exophthalmos is often associated with pain and subjective tension in the eyes; milder cases are usually free from pain and other sensations. The lids are often dark and sometimes swollen; the bulbs are glistening, sometimes there is excessive secretion of tears. From the diminished motion of the lids and the lessened sensitiveness of the cornea, ulceration is favored. The pupils rarely show alterations, aside from accidental conditions. Mydriasis and miosis sometimes occur, with other symptoms of irritation of the sympathetic. This cannot, as a rule, be ascribed to pressure, but seems to be due to toxic processes.

Narrowing of the fields of vision has been noted, but Moebius considers it the result of an associated hysteria. Amblyopia, achromatopsia, paralysis of various ocular muscles have been described, rather as complications, however, than as part of the main disease. Tremor of the bulbs has been described in rare cases, also tremor of the eyelids on attempts at closing them.

Ulceration of the cornea, observed in one case by von Basedow, is a rare and dangerous occurrence. Von Graefe thought it more common in men in advanced age, and Jessop found 7 men affected to 18 women (instead of 1 to 4 to 10). It occurs in some patients apparently not severely ill. Cataract operations are said to be badly borne by patients with Graves' disease. Circumscribed œdema, ephemeral or periodic, pigmentation of the skin, and also vitiligo, may occur on or near the eyelids.

Nervous System.—The nervous system in Graves' disease is always abnormal, and in many patients it is the seat of the earliest symptoms. This is spoken of as "nervousness," and on closer inquiry appears often as mental irritability, excitability, or restlessness. Sometimes neurasthenic conditions can be traced back long before Graves' symptoms, either as irritability or mental fatigue from trifling causes, with loss of memory and intolerance of company or of strangers. Some patients are depressed, apprehensive, or have morbid fears, even dread of death. Others have morbid exaltation, with capacity for considerable mental labor. The mental condition is sometimes well described by the expression "chorea of ideas." Murray mentions a patient who learned Turkish, and the writer has known several who finished courses in medicine in the usual time. Severe mental alterations may occur. True psychoses are rare, but Basedow's first two patients were considered demented. Depression and exaltation occur and may alternate. One patient of the writer's acted like a person in mild cheerful alcoholic inebriety. In severe acute cases there may be stupor or mania, with confusion of ideas and hallucinations, either visual or auditory. Delirium of persecution and grandeur occur, also suicidal and homicidal mania. Recovery is possible, but the outlook is generally grave. In less severe cases there are various paresthesias, such as globus, throbbing, vertigo, and formication. In one case

the writer saw temporary paraphasia. The sensation of heat may be complained of when the skin is not red or warm. Loss of sleep is often complained of, and really exists in a large number of cases. Dizziness and faintness are not rare. Headache does not seem to be very common. Neuralgias sometimes occur in various parts of the body. Local twitching may be annoying, and also cramp, especially in the legs, at night. The tendon reflexes are not rarely increased, and spastic phenomena sometimes occur. Epilepsy has often been reported, but is, of course, only a complication. Ascending paralysis and multiple neuritis have also been observed.

Eppinger and Hess[1] have emphasized the preponderating effects of the vagus and sympathetic systems. In the former (vagotonic) tachycardia is slight but subjective heart symptoms severe; slight exophthalmos but marked lid symptoms; tendency to excessive perspiration, diarrhœa, hyperchlorhydria, eosinophilia, and dyspnœa. In the sympathicotonic cases there are opposite symptoms, with greater tendency to glycosuria. There are many suggestions of value in this work, but it must not be supposed the antagonisms are always present and complete.

Muscles.—A characteristic symptom of Graves' disease is tremor, mentioned by previous authors, especially Charcot, and fully investigated by P. Marie (1883). It varies much in force, from a fine, barely perceptible tremor up to a distinct shaking of extremities, head, or the whole body. When mild it is best seen in the hand and fingers when outstretched, or in movements like sewing or drawing a straight line with pen or pencil. By having the patient draw a line slowly in a measured time, a useful record of the tremor may be obtained. The tremor is rapid and rhythmic, 8 to 10 in a second. It occurs in almost all cases, but may be temporarily absent. Choreic movements occur occasionally. Tetany has sometimes been a complication.

Muscular weakness is another very characteristic symptom. It is so rarely absent that it is strange that Askanazy's finding of muscular atrophy and degeneration has not been more widely controlled. Fr. v. Müller gives some comparative measurements showing the degree of the weakness.

	Basedow's Disease.		Normal Woman.	
	R.	L.	R.	L.
	Kilogram.		Kilogram.	
Shoulder, adduction	3.8	3.6	13	12
Shoulder, abduction	1.9	1.5	15	12
Elbow, flexion	4.8	4.0	30	25
Elbow, extension	5.6	4.8	18	14
Finger, flexion	6.5	5.5	20	18
Hip-joint, flexion	4.6	4.1	30	
Hip-joint, extension	5.1	4.6	35	
Hip-joint, adduction	4.5	4.5	15	
Hip-joint, abduction	4.0	4.0	15	
Knee, flexion	7.1	6.6	30	
Knee, extension	13.4	12.1	40	

Paralysis and even atrophy of certain muscles, such as those of the neck, arms, hand, and peroneal group, have been observed. It is probable

[1] *Zeitsch. f. klin. Med.*, 1909, Band lxviii.

the nervous relations of the paralysis differ in various cases, sometimes being central (optic nucleus in the case of eye muscles); in others the process is purely muscular.

A striking but comparatively rare sign is giving way of the legs (Charcot), but weakness of the legs noticed in walking or climbing stairs is very often mentioned early. It can go on to paraplegia, without bladder symptoms, loss of sensation, or marked atrophy, but with loss of skin and patellar reflexes. A similar condition has been seen in myxœdema (Mackenzie, Revilliod). Hemiplegia and monoplegia have been described. In many cases with nervous complications the relations have been very obscure. In such cases the diagnosis of Graves' disease has been made when the symptoms were confused beyond accurate recognition. Tachycardia and tremor in moribund patients are not necessarily signs of the disease, even if an old goitre is present.

The Skin.—The skin shows many and various changes. It is usually warm and moist. The warm skin is usually associated with a feeling of subjective warmth and a tendency to feel better in cold weather. Sweating is sometimes excessive, especially under excitement. In the case of a teacher, the writer has seen pools of water form from the perspiration falling from his hands during a recitation. Partly from the moisture, partly perhaps from an atrophy of the skin, the resistance to the galvanic current is lessened (Chvostek, Vigouroux), but this is of no special diagnostic value. Dryness of the skin is suggestive of myxœdematous degeneration.

The skin of the exophthalmic goitre patient is often pale, even when the hemoglobin is not notably reduced. Some look normal, others have a more or less constant flush of the face and sometimes the neck. The finger-tips and nail beds are sometimes flushed. On examination of the thorax a diffuse mottled blush is often seen, usually fading soon, but easily brought on by touch or by embarrassment. Various degrees of vasomotor anomaly are shown by rubbing or scratching the skin, up to striking and lasting dermographism and urticaria. Pruritus is sometimes present. Circumscribed œdema is not uncommon, and may be ephemeral or periodical, or last a long time. Œdema of the extremities occurs often and in varying degrees. It is sometimes of high degree, and of unusually solid consistency. In one case it extended up to the body, during a period of severe symptoms, but disappeared with improvement of the other symptoms. Ascites occurs occasionally.

Vitiligo is sometimes present. A more common pigment anomaly is a brownish discoloration, from pale to dark, like sunburn, or the diffuse pigmentation of Addison's disease. It is usually more intense on the face and in places normally pigmented, or where pressure is caused by clothing. The mucosa is rarely affected. The pigmentation often fades as the other symptoms improve. Sometimes scattered areas of dark color appear on the skin. Many observers have described pigmentation of the eyelids, but it is neither constant nor early, and hardly deserves to carry the name of any of those who have mentioned it. In one case with pigmentation von Schrötter also saw lipomatosis of the lower extremities. Scleroderma has often been observed in patients with Basedow's disease.

Alopecia is not uncommon. David Walsh[1] finds a band of baldness across the frontal region with a "bay" running back from each end, often described as a "high forehead," associated with a tendency to exophthalmic goitre. The writer believes the condition more suggestive of hypothyroidism. The eyelashes and eyebrows are also sometimes lost, adding to the strangeness of the patient's appearance. In one of the writer's patients the body hair all fell out with unusual rapidity under *x*-ray treatment. Others have noted spontaneous loss of body hair. Early graying of the hair is said to occur.

The Lymphatic Glands.—The lymphatic glands near the thyroid are always found enlarged at operation. In many cases the superficial cervical glands are palpably enlarged, and in a small proportion the axillary and inguinal glands also. The spleen is often enlarged. The enlargement of the thymus, so often noted at autopsies, is rarely discovered clinically. Careful examinations should be made in every case by percussion, palpation, and, if possible, the *x*-rays. Negative findings do not exclude enlargement.

The Blood.—There is often a mild simple anemia or chlorotic anemia. Chlorosis is sometimes present as a complication. Increase of the lymphocytes and large mononuclears is very frequent, either relative or absolute, with decrease of polynuclears and without increase of total leukocytes. A. Kocher thinks the lymphocyte increase is proportional to the severity of the disease, but sometimes absent in severe cases. In these the prognosis is serious. In improvement from any form of treatment the leukocytes usually return to a more normal formula. Increase of eosinophiles, sometimes present, is looked upon by Eppinger and Hess as evidence of irritation of the autonomous nerve.

The Alimentary Canal.—There are many symptoms on the part of the alimentary canal. Anorexia is uncommon; the appetite is more often good, even voracious. Thirst may be increased. Salivation sometimes occurs early and may be paroxysmal; dry mouth is rarer. Attacks of vomiting sometimes occur, especially in severe cases. In the latter the vomiting may be severe and exhausting, though rarely painful. The secretory and motor functions of the stomach in mild cases are often good, but sometimes the free hydrochloric acid and pepsin are reduced, and there is premature emptying of the contents. Excess of mucus is sometimes present. Postmortem, atrophy of the gastric mucosa has been observed.[2] Diarrhœa is a common symptom, occurring in about one-third of the cases, sometimes in paroxysms or "crises," with or without vomiting. It may be dietetic, or may be due to gastric hyposecretion with hypermotility. Often the diarrhœa has the features of a toxic process, coming on suddenly with abdominal pain, and with watery stools to the number of five, ten, fifteen, or even forty a day. It may stop as suddenly as it began, even without treatment, or may last several days in spite of opiates, astringents, and intestinal antiseptics, with or without a preliminary purge. Sometimes the passages are choleraic, at other times bloody. They may show good digestion, or none at all. Bile

[1] *Proc. Roy. Soc. of Med.*, May, 1908, p. 195.
[2] Miesowicz, *Wien. klin. Woch.*, 1904, p. 1206.

coloring matter is often deficient. Between the attacks the bowels are often constipated. Moebius reports a case in which diarrhœa, headache, and insomnia were the earliest complaints, although the patient had a goitre and tachycardia. Tremor and other signs developed later. The diarrhœa has been considered toxic, but more recently has been ascribed to irritation of the vagus (Eppinger and Hess). Schmidt and Salomon, and Falta, have described cases with fatty diarrhœa and with lowered carbohydrate tolerance. Inhibition of the internal secretion of the pancreas seems probable.

Respiratory Organs.—*Dyspnœa* is often complained of, and can be noticed, even aside from exertion, in a considerable proportion of cases.[1] It is often associated with deficient expansion of the thorax (Bryson's sign), which may be as low as 1 to 1.5 cm. Litten's sign often gives evidence of imperfect contraction of the diaphragm. Dyspnœa and deficient expansion may most readily be explained by muscular weakness. Hofbauer and Sharp report crises of dyspnœa. In some cases the dyspnœa is partly, at least, due to pressure on the trachea, sometimes to pressure on the recurrent nerve. A dry, sometimes ringing cough, hoarseness, and aphonia may be present. Pulmonary hemorrhages have been observed.

The Kidneys.—The kidneys are rarely severely affected, but albuminuria with hyaline casts is usually present when the heart is much dilated. The urea, total nitrogen, uric acid, and phosphates are increased. In many cases alimentary glycosuria has been observed; in some, diabetes mellitus. Polyuria is not infrequent, and may often be explained by the polydipsia and large meals; in other cases it may be of nervous origin.

The Sexual Organs.—On the part of the sexual organs the changes are not, as a rule, prominent. Loss of sexual power occurs in men occasionally. Menstruation is usually in proportion to the condition of the blood and nutrition. Early atrophy or hypoplasia of the uterus and ovaries is a rare occurrence. The mammary glands are usually more or less atrophic, but sometimes seem to have become larger during the disease. This may be related to the lipomatosis, sometimes present in other parts of the body. In Basedow's male patient the mammæ were swollen and hyperemic, and secreted colostrum. Pregnancy is often beneficial to patients with exophthalmic goitre, though in general it should not be recommended unless the condition is fairly good and seeming to improve.

In some cases postmortem the bones have been found soft, and in a patient with kyphoscoliosis Koeppen made a diagnosis of osteomalacia. The same author reports dental caries. The writer has not noticed a special tendency to that, nor to the deformities of bones or (except in one case, with scleroderma) the pointed fingers described by Revilliod. Chronic and also intermittent arthritis have been described in rare cases. Holmgren[2] has made a study of cases in young people with unusual growth in the long bones. In 89 cases before the fifteenth year the majority showed excessive growth.

[1] See Hofbauer, *Mitth. a. d. Grenzgeb. d. Med. u. Chir.*, 1903, Band xi.
[2] *Nord. Med. Arkiv.*, 1909, Band ii, Heft 2, Nos. 5, 8.

Emaciation.—Emaciation is an almost constant and suggestive sign. The loss of weight is rarely less than fifteen or twenty pounds when the patient is first seen, and may be thirty or even sixty or more. In one of Mannheim's cases it was ninety-three pounds in ten months. It may amount to one-third or even half the original weight. It often begins before diarrhœa and vomiting, but these may make it much worse. Huchard has well spoken of "crises of emaciation." Sometimes there is almost as marked and rapid gain—thirty-three pounds in ten weeks in one patient, in whom sixty-two had been lost in one year. The gain may take place notwithstanding diarrhœa. In mild cases there may be a gain in weight—thirty-eight pounds in two years in one patient. The emaciation is evidently due chiefly to thyroid intoxication, and this helps to explain why it varies so much in different cases.

Fever.—Although the feeling of subjective warmth, or even heat, is very common in exophthalmic goitre, actual fever is rather rare, except in the fatal cases. Bertoye,[1] who has made the most extensive investigations in this respect, finds high temperature during long or short periods, and of different degrees of severity. In some cases it resembles that of typhoid fever, and is benefited by cold baths. The other symptoms of fever are sometimes present. In the writer's experience actual fever has been rare, but sometimes with hyperthemia (107° in two cases, one fatal; another mistaken for malaria). W. G. Thompson has seen fever of 101° to 104° F. in 14 out of 43 cases, in some above 104° F. "It is of septic type, oftenest remittent, but sometimes intermittent, and always irregular and occasionally remaining elevated three or four degrees for several consecutive days. The duration of the fever varied from a few days to several weeks. Often it lasted for ten days or a fortnight, in one case for forty days, and in another thirty-eight days." Bertoye thought the fever due to nervous and infectious causes combined. It would seem most probable that either thyroid toxemia or secondary infection is the cause. It sometimes occurs after removal of thyroid tissue.

Metabolism.—The hyperthyroidism is shown in exophthalmic goitre by increased metabolism. This is chiefly responsible for the emaciation. CO_2 production and oxygen consumption are increased; proteids, carbohydrates, phosphates, and calcium also.

Complications.—In such a chronic disease as this any and all possible complications may be expected, but only the most peculiar or striking ones need be mentioned. Diseases of other ductless glands are of the greatest interest, because many of their symptoms may be present in cases of exophthalmic goitre. Among them may be mentioned acromegaly, described by Ballet and Holmgren. Myxœdema is a sequel rather than a complication, although the symptoms sometimes run parallel for a time. Chlorosis is sometimes observed; Neusser has reported a case of pernicious anemia; pseudoleukemia has been reported, and deserves careful investigation whenever suspected. In one such case the writer found a distinct leukemic change in the characteristics of the lymphocytes. In Neusser's case of Basedow's disease with pernicious anemia,

[1] *Étude clinique sur la fièvre du goitre exophthalmique*, Lyons, 1888.

atrophy of the liver was found postmortem. Jaccoud has reported a somewhat similar case, with icterus and hemorrhages and fatty degeneration of the liver. Neusser in this connection calls attention to the relation between the thyroid and the liver. Stockton and Woehnert[1] report a case of thrombosis of the superior vena cava and innominate veins.

Hysteria in all its forms may be associated with Graves' disease. Many of the cases of so-called epilepsy, perhaps also those of "chorea," belong here. Moebius, and more recently Alfred Gordon, have called attention to the combination of Graves' disease and paralysis agitans. Tabes dorsalis is often a complication, and one of special interest on account of the possibility of a syphilitic origin of the thyroid alteration. Abrahams has reported the recovery of a case of postsyphilitic Basedow's disease. L. Lévi has called attention to the frequency of Basedow's disease among tuberculous patients—13 out of 170, besides 14 incomplete cases. Arthritis is an occasional complication.

Clinical Forms.—There are various classifications of exophthalmic goitre and many are satisfactory, provided their limitations are understood. Cases are often spoken of as primary or secondary, the latter when the symptoms occur in the subject of a previous goitre, the former when the goitre develops with or after some other symptoms. But often there is a goitre unknown to a patient, or even to the physician. With greater care the goitre could often be found in such cases. All surgeons speak of the frequency with which, at operation, thyroids supposed not to be enlarged are found distinctly enlarged, and these cases can often be recognized by finding a thrill or murmur over the gland, evidence of vascular anomalies. From the anatomical and clinical standpoint there is some advantage in Kocher's classification: Vascular goitre; Basedowized goitre; Basedowian goitre. The differences are gradual. Even if in some cases there is a history of previous goitre, this does not indicate that the goitre as such causes the other symptoms, the latter are not secondary in that sense. In both primary and secondary cases the symptoms occur in the same general order, and although in the former the course is often more acute, there are many exceptions.

Acute and chronic cases are distinguished according to the length of time they last, the former ending in a few weeks or months, although some would term "acute" cases lasting a year.

According to the number of symptoms cases are spoken of as complete, incomplete, abortive, rudimentary, or fruste. The terms most often are used with reference to the chief symptoms, especially those longest known. In a disease with so many symptoms the question of completeness must depend largely upon the accuracy of the observations and the care in noting them. As at present used, we do not know in a given case of "incomplete Graves' disease" whether it lacks, *e. g.*, exophthalmos or goitre, or has none of the classic signs, but possibly has nervousness, emaciation, and tachycardia. Some further qualification would be useful in such cases. Acute cases are often apparently primary and with many symptoms. Many, if not most of these, if carefully examined

[1] *New York Medical Journal*, 1908, lxxxviii, 145.

will be found to have had distinct signs months or years before the acute appearance of the striking symptoms.[1] Perhaps the same is true even of the peracute cases, of which examples are found in literature, in which the symptoms come on in a few hours. From the nature of the alleged causes, overexertion, sexual excess, or excitement, as in one of von Graefe's cases, fright, etc., it seems certain some very unusual process must have been present. In some cases the onset is abrupt, but is soon followed by a rapid improvement. In the great majority of cases we can find by careful inquiry a long history, up to twelve or fifteen years, of some slight symptoms. Then, usually after some definite occurrence, such as shock, exertion, infection, this latent stage passes into one or more important symptoms. This is often followed by a relative improvement. Renaut has suggested the useful classification of a latent stage, stage of intolerance, and stage of tolerance. It is characteristic of the disease that exacerbations tend to develop rapidly but to subside slowly, and to occur at longer or shorter intervals, sometimes without, but usually with, a discoverable cause.

The early idea that the disease was characterized by a "triad" of symptoms gives way slowly, notwithstanding the long array of symptoms that occur in general, and the number that can be observed in many cases. As has been said before, enlargement of the thyroid is often present early and almost never absent. Nervousness or tremor is almost as frequent. Heart symptoms are also rarely absent, although subjective palpitation is by no means essential. Acceleration of the heart rate, taking into account the age and constitution of the patient, is rarely missed. In cases of very infrequent pulse, as 50 to 60, it is important to know whether the heart beat is equally slow. It is possible in a Basedow's case to see a pulse of 50, 60, or 80 noted, by reason of an arhythmia of some kind. In one case, with the pulse noted as 52, there was a regular alternation due to extrasystole. Careful palpation revealed the small beat, but a tracing was necessary to prove it was a weak systole and not a dicrotic wave. In acute cases heart symptoms are usually early and severe—tachycardia, dyspnœa, and irregularity; besides these, vomiting and diarrhœa, fever, sweating, vasomotor changes in the skin, and pigmentation are very often present. Some symptoms occur only in severe cases or severe stages, *e.g.*, fever, hemorrhage, delirium, paralysis.

Diagnosis.—This is difficult only in cases with few symptoms, and especially when those are mild. Cases with slight tachycardia and mild nervous disturbance are often overlooked because a careful examination is not made. If the tachycardia does not subside in a short time with rest, if there is no ordinary heart lesion, and if there is characteristic tremor, with Stellwag's and Moebius' signs, emaciation, increased perspiration, and poor sleep, with dyspnœa on slight exertion, the diagnosis can usually be made without difficulty. In goitre districts a goitre is not in itself a valuable sign, but if there are vascular anomalies in the thyroid or over it, as described in the preceding sections, the diagnosis can be made. The diagnosis of "goitre heart" in such cases is by no

[1] Arneill, *Jour. Amer. Med. Assoc.*, 1900, xxxv, 880

means as safe or rational as that of Basedow's disease. Exophthalmos of the characteristic kind is hardly possible to refer to anything else, but cases of orbital tumor or aneurism of the orbital artery are too often mistaken for exophthalmic goitre. Careful examination of the eyes and the other symptoms cannot leave one long in doubt.

The confusion of mild cases of Graves' disease with neurasthenia cannot withstand the complete physical examination and study that every suspected patient with neurasthenia should have.

"Iodism" can be recognized by the history, but in all such cases careful investigation should be made in order to determine if the so-called iodism is not really a hyperthyroidism that needs the same kind of treatment that cases of Basedow's disease require.

Kraus suggests that determinations of the respiratory metabolism (increase of CO_2 and N) by the use of the Zuntz-Geppert apparatus may be useful in diagnosis. Fr. v. Müller observes that this is too complicated, and that careful tests with iodine would be better; patients with hyperthyroidism show their intolerance by emaciation and tachycardia, even in small doses.

Prognosis.—Exophthalmic goitre has been defined as a disease from which patients never recover and never die. It would be more accurate to say that few recover and some die. Relative recovery, however, is not rare. In this the patient becomes able to carry out the usual duties. He, or more frequently she, is not perfectly well, but about as well as patients with mild neurasthenia. Many years may pass with freedom from severe symptoms, but with some nervousness, slight increase of pulse rate, and exophthalmos with Stellwag's and often other eye symptoms. More complete recovery may be expected when operative treatment is carried out early. The disease is essentially chronic, a duration of ten, twenty, or more years being not uncommon. Exacerbation may come on suddenly, due to various overexertions or infection.

The actual death rate is impossible to fix, on account of the great variation in the severity of the symptoms, the fact that a relatively large proportion of severe cases is reported, and that death is often due only indirectly to the disease itself, often to complications or accidentally associated diseases. Buschan's figure, 11.6 per cent., is of limited value only, and a better index of the danger than higher figures in chronic figures. Hospital statistics, showing a death rate of 30 per cent. in acute cases, do not apply to the majority of cases found in general practice.

Among the causes of death cardiac weakness is most important. Next comes exhaustion from vomiting and diarrhœa, fever, and other toxic phenomena. Pneumonia and tuberculosis are common terminal diseases. Death after operation is usually due to cardiac failure.

Treatment.—The number and variety of modes of treatment for exophthalmic goitre, and the confidence with which the most diverse methods are lauded prove that something more is effective in favorable cases than medication. The essential things we may believe are the frequent tendency of the disease to improve, the general measures that are carried out with the other details, the expectation of help on the part of the patient, assisted by the relief of various symptoms, either from general

or special treatment. In the absence of a causal treatment it is proper to begin with the empirical method.

The muscular weakness, the condition of the heart, and the nervous irritability, as well as the increased metabolism in exophthalmic goitre all indicate the necessity of rest. This must be adapted to the patient. In severe cases or stages the most rigid details of the rest cure are necessary. These need not be described here, but the application of rest in milder cases requires further consideration. General statements to patients are useless; it may be impossible to secure rest in bed at fixed hours, and in many cases the rest can be obtained better in other ways. Long hours of sleep are beneficial, and the patient should retire as soon as the work of the day is over. Late hours should be avoided as much as possible but when they appear necessary should be preceded and followed by rest of sufficient length. In the daytime the patient should lie down rather than sit, and sit rather than stand, but there is usually no advantage in sleeping in the daytime, and if done it often prevents sound sleep at night. It is possible for patients to take even several hours of rest daily on a couch, cot, or even the floor, convenient to the usual working place, when going to bed would either be impossible or would involve more work than could be made up by the rest following. So far as possible stair-climbing should be avoided.

Exercise should not be permitted in the beginning of treatment. Massage and passive exercise may take its place for a time. After the necessary improvement has been obtained gradually increased exercise should be encouraged. Patients must always be plainly instructed regarding exercise, and its amount should be based upon the necessary work done by the patient. Both work and exercise should stop short of fatigue on the whole, and at any time of the day.

Mental rest is just as important as physical rest. It can be secured in patients who do not need rigid seclusion by avoiding all unnecessary or harmful activity. Necessary or congenial occupations can usually be carried on, cheerful company should not be shunned, but all exciting and depressing occupations should be given up. Reading, sewing, and all diversions and amusements need to be investigated by the therapeutist with reference to the individual. Dancing is often injurious. Exhausting tours are dangerous, but leisurely travel is often good for patients without severe symptoms.

Hydrotherapy has been used with benefit. In most cases it is enough to see that bathing is done to the necessary extent, and to prevent exhausting and depressing baths. As regards clothing, tight collars and excessive lacing should be avoided.

The *diet* should be as varied as possible, and in amount such as to increase the weight if not to bring it to normal. The scales should be used regularly as a guide to progress. All anomalies on the part of the stomach must be corrected. Overfeeding must be carefully avoided. Frequent smaller meals are usually preferable to few large ones. It is not necessary to exclude meat. Milk, buttermilk, and fermented milk are all useful, but coffee and tea must not be taken in excessive quantities. All indigestible and stimulating foods and condiments should be avoided.

Alcohol should not be used if it causes symptoms, and is not necessary in any case.

The patient should get as much fresh air as possible, and as this cannot be taken in sufficient amount in the usual way, by walking or driving, the patient should spend as much time as possible reclining out of doors, well protected from cold and wind. The bed room should be well aired, or the patient may with advantage sleep out of doors. In the latter case it is essential that sleep be not lost by early waking from light that can be excluded. Climatic treatment is rarely necessary. If patients desire a change, moderate elevation, pure cool air, and freedom from high winds should be sought. The seashore is usually not favorable, and high elevations are also often unfavorable for the heart and the nervous symptoms. The physical and mental occupations must be carefully ordered at climatic resorts.

The general measures are beneficial to many symptoms, but other details are often necessary. Tachycardia and palpitation usually subside quickly under rest, although they may have resisted all medicinal treatment. In general, no drug should be given for the heart in the beginning of treatment unless rest is secured. If rest alone does not quickly reduce the pulse rate, a light ice-bag should be put over the heart, constantly or intermittently, according to the effect. If there is much vascular excitement in the thyroid or the cervical vessels, an ice-bag or coil may be applied there.

Of cardiac stimulants, digitalis should only be used when there is cardiac weakness, and even then must be carefully watched. Arhythmia and gastric irritation may be caused by it. If necessary to give it, it should be omitted every other day, or every third or fourth day, according to the conditions. In mild cases strophanthus (the tincture, 5 to 10 minims) gives good results and is much more easily borne than digitalis. Strychnine also is useful in these cases. Belladonna or atropine is thought by some to lessen the overactivity of the thyroid. They have also been used to lessen the excessive sweating, but other measures are more useful.

For nervousness, restlessness, and insomnia, rest, fresh air, a cool bedroom, and comfortable bed are more important than drugs. A neutral bath (95° to 96°) of fifteen to twenty minutes may be given before retiring. Sometimes a hot drink, or a hot water bag to the feet, possibly also one to the epigastrium, proves beneficial. If restlessness resists these measures, a full dose of bromide should be given at bedtime, one dram of the sodium salt, repeated in an hour if necessary. This is much better than a smaller dose repeated night after night. Pure hypnotics are rarely necessary. Opiates should never be used in cases that have any chance of survival. The severe psychical disturbances, mania and delirium, require treatment as under other conditions. Asylum treatment is rarely necessary.

For the stomach and intestines, regulation of diet suffices in many cases. Strychnine is sometimes useful as a stomachic, or small doses of quinine may be given before meals. Constipation should be avoided by diet, water, and regular habits as far as possible. As a further aid, a mild laxative, such as cascara sagrada or sodium phosphate, should

be used in appropriate doses. Sodium phosphate has been considered a sort of specific by many besides Trachewsky and Kocher, but the writer has never seen evidences of that, even when given in doses of 20 to 80 grains from one to three times a day. Many use mercurials at short intervals. With care and milder measures they are unnecessary.

In gastric and intestinal crises, the stomach and bowels should be evacuated by lavage, cathartics, and enemas. Simple diet, such as gruel and albumin water, should be used for a few days. Bismuth and antiseptics, such as salol, often seem beneficial, but opiates and astringents should be avoided as much as possible. The anemia rarely requires iron or arsenic. They have no specific action upon the disease, but may be used for positive indications on the part of the blood. Pallor is by no means evidence of anemia in patients with exophthalmic goitre, nor is flushed skin a sign of plethora.

Fever, if present as a complication or in severe cases, should be treated by tepid sponging, tepid full baths, or cool full baths, according to the indications.

Irritation and ulceration of the cornea or conjunctiva, from exposure, should be treated with boric acid solutions in the beginning. Special treatment should be applied if the treatment is not quickly beneficial. Tarsorrhaphy, for cosmetic or protective purposes, has never made itself a place. Section of the sympathetics may be of value. Fortunately the most severe exophthalmos is rare. Other complications should be treated according to the special rules for such conditions.

Iodine and iodides have been used a great deal in the treatment of exophthalmic goitre, and often reduce the size of the thyroid. Some patients improve generally under or after the treatment. On the other hand, others are made worse, having palpitation, headache, nervousness, etc. It is obvious that the diminution in the size of the gland under iodine does not indicate, necessarily, a reduction of the process that causes the hyperthyroidism. If no bad effects are produced, it may be useful to affect the simple goitre by careful iodine treatment, but it should always be remembered in this disease that iodine may be the "drop that makes the vessel run over." Breuer even warns against iodoform on dressings over thyroid wounds. The use of ointment of red iodide of mercury, once relied upon to reduce the size of the gland, is now almost wholly abandoned. Injections of iodine, iodoform, and the like to reduce the gland are more dangerous than surgical operations.

Electricity has been much used, and excellent results have been reported. It may be admitted that under the use of weak currents many symptoms subside, but it is instructive to see that while one operator uses a certain kind of current, as the galvanic, others insist that only the faradic current is useful, still others static, high frequency, or some other variety. It seems that the chief benefit is rather due to the associated general measures, or to suggestion from belief in a potent and mysterious means of cure.

Suggestion doubtless plays an important part in all successful methods of treatment of such a disease, and should be utilized in a rational manner, but hypnotic suggestion is unwarranted.

Röntgen rays have been used with varying results. C. H. Mayo thinks they lessen vascularity, induce sclerosis around the gland, and so diminish the risk of hemorrhage at operation. R. Freund[1] has recently reported some favorable results, with a review of the literature. F. R. Cook[2] relates the most far reaching effects. The writer has treated several cases, and, although local and general improvement sometimes followed, was not convinced that the treatment was of real value. The use of radium in the gland, as practised by Abbé, does not seem to have been distinctly beneficial, and is not likely to be widely imitated.

Organotherapy.—Very soon after the rise of modern organotherapy, thyroids, fresh and dried, and also iodothyrin, were used in exophthalmic goitre. With various preparations the goitre often becomes smaller, and in some cases other symptoms also improve, but in others they grow worse. According to the hyperthyroidism theory, the latter seems inevitable, unless the preparation is inert. There are some, however, who believe the matter not so simple. If altered secretion is the cause of the disease, the ingestion of a normal gland substance or its active principle may be capable of assisting the function of the gland until it becomes improved. Mackenzie also suggests that thyroid treatment may be useful in old cases with deficient secretion. On account of the lack of accurate knowledge of the strength of thyroid preparations and the danger of producing alarming symptoms, they do not seem at present advisable.

From the frequent finding of an enlarged thymus in exophthalmic goitre, and the idea that it might be compensatory, thymus preparations have been used by Mickulicz, S. Solis Cohen, O. T. Osborne and many others. Even before planned experiments, Owen, through the mistake of a butcher, fed a patient on thymus, and only discovered the error after the case had been reported as one of improvement under thyroid feeding. A number of patients have taken it without benefit, and more experimental work should be done before it is prescribed.

A wholly different method was originated by Ballet and Enriquez (1895), who tried to neutralize the poison of the Basedow thyroid by giving the serum of thyroidectomized dogs. Similar experiments were made with the milk of thyroidectomized goats (Lanz) and sheep, the blood of a myxœdema patient (Burghart), the thyroid of a cretin (Moebius). At present the available remedies of this class are: Antithyroidin Moebius (dose 8 to 60 gtt., 0.5 to 4 cc., t. i. d.), prepared from the serum of thyroidectomized sheep and preserved by the addition of 0.5 per cent. carbolic acid; rodagen (75 to 150 grains, 5 to 10 grams a day), prepared from the milk of thyroidectomized goats and triturated with milk sugar; and thyroidectin (dose 5 to 50 grains t. i. d.), made from the blood of thyroidectomized sheep. The fresh milk of thyroidectomized goats, from six weeks after operation, has also been used, but many patients acquire a disgust for it. The milk of one goat, up to three pints a day, may all be taken by the patient.

Under treatment with all these preparations the changes observed are

[1] *Münch. med. Woch.*, 1907, No. 7.
[2] *Jour. Amer. Med. Assoc.*, 1908, i, 758.

about the same. The enlarged thyroid becomes smaller and softer. Of the other symptoms, the most distinct effect is seen on the heart, as in all other methods of treatment. Irritability and weakness are sometimes improved, but very often they are not. A few patients quickly begin to improve, but in the majority the progress is slow. The dosage is of course a matter of guesswork. We do not know how much toxin we have to neutralize, nor how much antidote there is in a given amount of the remedy. The customary method is to increase the dosage as rapidly as possible, beginning with the minimum, and adding as much every day until there is a marked improvement or signs of intolerance, and then to decrease, continue, or stop altogether, according to the condition. Rodagen and antithyroidin sometimes become objectionable, the former from its peculiar odor, the latter from its phenol. Thyroidectin is less disagreeable. It, and probably the others, seem to form a habit, so that patients who are not greatly benefited by it find it difficult to abandon the drug. All the preparations are expensive.[1]

A different method was adopted by Murray,[2] and by Beebe and Rogers.[3] The latter, who have carried out a large series of experiments, obtained a serum by injecting the nucleoproteid and the thyroglobulin from thyroids of Basedow patients (obtained at autopsy) into rabbits. Later, thyroids removed at operations were used. Besides the "pathological" serum, a "normal," "antitoxic," or thyroidal cytotoxic serum was obtained by using the nucleoproteid and thyroglobulin of normal human thyroids. It is too early to speak of the effects of this class of preparations; Rogers and Beebe take a very cautious and conservative standpoint. The preparation of the serum is attended with obvious difficulties, and those who wish to repeat the observations should have a sound experimental basis.[4]

Surgical Treatment.—In the last few years the results of the surgical treatment of exophthalmic goitre have forced the importance of such measures upon our attention. At first glance it seems reasonable that if there is hyperfunction, removal of the redundant tissue or its reduction in size would cure the disease. When, however, we remember that we cannot remove the whole of the thyroid gland, that we cannot tell, when we take out a part, whether the remaining portion is not relatively more dangerous, and when we recall how hypertrophied tissue may keep on growing or grow more rapidly if partially removed, it becomes clear that the theoretical basis of the treatment is very incomplete.

Since Rehn first operated, in 1884, many hundreds of operations have now been made, and in a large number sufficient time has elapsed to give a fair idea of the results, which in large series reach as high as 75 per cent. of symptomatic recoveries. The operations include all kinds of cases, recent ones as well as those of long-standing, severe ones and mild ones. After the first few days immediately following operation

[1] Bulkeley, *Boston Med. and Surg. Jour.*, 1907, clvii, 626.
[2] *The Lancet*, 1905, ii.
[3] *Jour. Amer. Med. Assoc.*, February 17, 1906, pp. 484, 487; *Trans. Assoc. Amer. Phys.*, 1906, pp. 513, 549, 577 (discussion); *Archives Inter. Medicine*, 1908, p. 297.
[4] See also Ewing, *New York Medical Journal*, 1906, lxxxiv, 1061.

there is usually a marked improvement, first seen in the tachycardia and other heart symptoms, soon after in the tremor and other nervous symptoms. Even the exophthalmos sometimes disappears, although in cases of long duration it cannot be expected.

As to the thyroid, the part left in does not always hypertrophy. Many operators, including Kocher, Reverdin, Poncet, Woelfler, and C. H. Mayo, say that it contracts. In some cases, however, hypertrophy occurs, with return of the symptoms, and sometimes requires a second operation.

Recovery, of course, does not always occur. Death ensues in a proportion varying partly according to the condition of the patients treated, but chiefly with the skill and experience of the operator. Kocher had 9 deaths out of 254 patients, 3.5 per cent., in his early work. Mayo has had 278 operations between deaths.

As regards the selection of cases, an important factor bearing on the completeness of the recovery is the condition of the patient. Cachectic patients, with advanced heart weakness and extreme exophthalmos, should not be urged to undergo operation, although even they may be helped. It is better to operate early in patients not distinctly improved by thorough treatment with rest and other measures, or in those who are not able to take such treatment, at as early a time as possible. Special indications are severe symptoms, especially toxic symptoms like tachycardia, and loss of strength. Local signs, as of pressure, or suspected adenomatous change, also indicate operation.

The operations most practised now are partial resection, or ligation of two or three of the thyroid arteries. Crushing, ligating en masse, exothyropexy, or open resection have no advantages, and are not practised by the operators of greatest experience. Sympathectomy alone has sometimes given good results, but also many failures, not always reported, and is now abandoned by operators of experience. The chief danger in thyroid operations is from heart failure. This is to be prevented, so far as possible, by getting the patient in the best possible condition by rest, the ice-bag, and cardiac tonics. C. H. Mayo does not operate if the pulse is above 130, or varying in force and frequency, or if there is anemia or œdema. In such cases he has treatment with *x*-rays and belladonna carried out. According to Kocher, high blood pressure is not a contra-indication, but cases with low pressure need careful treatment before and after operation.

Symptoms of hyperthyroidism, tachycardia, bounding pulse, sleeplessness, nervousness, vomiting, and diarrhœa sometimes occur in a few days following the operation. This sequence has been explained in various ways, especially by the absorption of thyroid secretion. It varies in frequency in different clinics. McCosh never saw bad results from handling the goitre, but saw a case, fatal within twenty-four hours, in which the superior thyroid arteries were ligated, without manipulation of the thyroid gland. Mayo points out that in these patients other operations may bring out hyperthyroidism. Adrenalin, atropine, and morphine can be used in the treatment of the condition. Kocher, who ascribes the symptoms to hemorrhage and absorption of toxic blood, says it can

be almost entirely avoided by care in technical details. Capelle's[1] suggestion as to the importance of the thymus has been most valuable, but many more observations must be made before Garre's operation of thymectomy can have a definite place in the treatment of exophthalmic goitre.

The danger of tetany is now largely avoided by care in the operation. The same is true of injury of the recurrent nerve.

The object of resection is to remove all excessive tissue. Since Halsted recommended the removal of as much as possible I have seen great benefit from it, and so far no bad results. If myxœdema follows, thyroid treatment can be carried out.

As the operation is one that should only be performed by surgeons of experience and knowledge of the special features, it is not necessary to describe the technique. Certain details are matters of choice. Kocher recommends local anesthesia; Mayo, general anesthesia with ether. In exophthalmic goitre the thyroid is rarely large enough to make general anesthesia especially dangerous, and on account of shock a general anesthetic seems desirable. Coughing is an undesirable sequel, but occurs sometimes even with local anesthesia. Crile's anoci-association method may sometimes be useful, but few patients require the more psychological details. Vomiting and secondary hemorrhage are particularly dangerous, and the latter is to be avoided by the most careful ligation of vessels and observation of the wound afterward. Kocher and Mayo recommend ligation of the superior thyroid arteries in mild cases, or in severe ones as a preliminary. Ligation is not without dangers.

After an operation for exophthalmic goitre the general and hygienic treatment should be continued until the patient is as well as possible, and later the occurrence of symptoms should lead to a careful examination, in order to discover and treat a relapse as promptly as possible.

[1] *Beitrage z. klin. Chir.*, 1908, lviii, 353; *Münch. med. Woch.*, September 1, 1908.

CHAPTER XXIII.

ATHYREOSIS. ATHYREA. ATHYROIDISM. HYPOTHYROIDISM. CRETINISM. MYXŒDEMA. THE PARATHYROID GLANDS.

By GEORGE DOCK, M.D.

The development of our knowledge of diseases due to loss of thyroid function began with the observations and reports of Gull and Ord, the recognition of the resemblance of cachexia strumipriva to myxœdema (Reverdin and Kocher), the experimental work of Schiff, Semon, Horsley, and others in the latter part of the last century. The implantation experiments of von Eiselsberg and Serrano and Bettencourt were soon replaced in treatment by the hypodermic method of Murray and the less troublesome and equally efficient internal administration, demonstrated by Howitz, E. L. Fox, and H. Mackenzie.

The coincidence of goitre and cretinism had been known since the time of Paracelsus (1616). From the end of the eighteenth century, and especially in the middle of the nineteenth, there was wider attention to the subject on the part of philanthropists and statesmen, but accurate study was not at first correspondingly increased, and under the term "cretinism" an inextricably confused series of cases—true cretins, rachitic dwarfs and idiots of all kinds—was thrown together. Sporadic cretinism was recognized early (Curling, 1850, Fagge, 1871), but it was not until myxœdema was fairly well known that the relation of all three forms could be accurately considered.

It is now accepted that goitrous degeneration is only one of many causes of loss of thyroid function. (Goitre, of course, does not always produce such conditions as we are about to describe.) Besides operative removal of a large part, functionally speaking, of the gland, various chronic atrophies, acute inflammation, and unknown factors play their parts. The effects upon the individual vary chiefly according to the age at which they operate. The earlier it occurs, the more the condition that results resembles cretinism; the later, myxœdema. Until recently tetany was included among hypothyroid or athyroid conditions, but it is now certain that the former has only accidental relations with loss of thyroid function.

The known results of hypothyroidism or athyroidism are:

1. Congenital myxœdema (congenital cretinism).
2. Infantile myxœdema (endemic and sporadic cretinism).
3. Spontaneous myxœdema of adults.
4. Postoperative myxœdema.
   - (*a*) From total extirpation of the thyroid.
   - (*b*) From almost complete extirpation.
   - (*c*) From atrophy of the gland after operation.

Many other conditions, especially certain forms of infantilism and obesity, were formerly classed as hypothyroid states, but they are now more accurately assigned to disease of the pituitary body, genital glands, or to polyglandular disease.

CRETINISM.

Endemic Cretinism.—Synonyms.—Endemic cretinism; cretinoid idiocy; cretinismus (Latin); Kretinismus, endemischer Kretinismus (German); crétinisme (French); cretinismo (Italian and Spanish).

The word cretin is usually derived either from (French) Chrétien, "innocent," or creta, "chalk;" the former referring to a widespread idea, the latter to the color of the skin. A more reasonable derivation is suggested by Bayon,[1] viz., from Rhaeto-Romanic cret, "cripple," "dwarf," cretin, "diminutive." As the same author remarks, athyreosis or hypothyreosis congenita or endemica would be preferable, since the term cretin is historically too general.

Etiology.—The etiology of endemic cretinism is as obscure as that of endemic goitre, with which it has such close geographical relations. The disease occurs in some but not all foci of endemic goitre. It is very common in the severe goitre districts of Europe, rare in many milder areas, like those of North America and England. All statistics in regard to the frequency of cretinism contain an error from diagnostic mistakes. The figures given under goitre, and the proportion stated for Carinthia and Salzburg (district), 293 and 276 per 100,000 population respectively, show the importance of the disease economically. When people migrate into such a district, goitre is likely to show itself in the first generation, cretinism in the later ones. Females are more often affected, in the proportion of 2 to 1. In goitre regions, cretins have goitrous mothers, or one or both parents are mild cretins. In some cases it seems as if congenital cretinism were derived from the mother, that occurring later, from the father. Not all goitrous parents beget cretinous children. In cretinous lands, marriage of two cretins is either sterile, or the infants are not viable.

Pathology.—Notwithstanding the close relations between goitre and cretinism, the exact pathology of cretinism is not yet agreed upon. Bircher especially opposes the view of identity of cause. Buschan considers cretinism a mixture of myxœdematous cachexia and degeneration. Since removal of a goitrous thyroid from a cretin may be followed by myxœdema, cretinism may be looked upon as an incomplete myxœdema.

The most striking anatomical feature of endemic cretinism is the abnormal skeleton. This is characterized by an arrested or retarded development of the bones, and not, as long believed, by early ossification. The retardation is due rather to a general disturbance of nutrition than to a specific interference with any of the processes of bone formation. The character of the bony change depends upon the period of growth

[1] *Beiträge zur Diagnose und Lehre von Cretinismus*, etc., Würzburg, 1903.

at which the disease begins. The earlier the thyroid change, the more marked the alterations of the bones. Bone development in cretins sometimes continues beyond the usual period, as shown by Wagner.

The skull is remarkable for its low forehead, deep and broad root of the nose, prominent malars, and prognathism. It may be large or small, broad or narrow. The spheno-occipital fissure is not closed prematurely, but has been found open at fourteen months (Langhans), twenty-four years (Klebs and Langhans), or cartilaginous at fifty-eight years (His). The bones of the extremities, and also the ribs, are short and thick, sometimes deformed. They may seem to resemble rickety bones, but they show no proliferation in the zone of development of the epiphyseal cartilages, and, on the other hand, exhibit delayed ossification (Langhans, Hanau, Bircher, Hofmeister, von Wyss, and others). In some cretins examined at advanced age (fifty to sixty years) ossification has been complete, but there is no rule. The pelvis is narrow. P. Müller, who finds narrow pelves especially frequent in Bern, ascribes them to cretinism. Histologically, cretinous bones are characterized only by the lack of ossification. Periosteal changes are not constant or peculiar.

Thyroid.—In the majority of cases of cretinism there are goitres of various kinds. Sometimes in the most severe cases the thyroid gland is absent (10 per cent., Wagner), sometimes small or normal, but never the latter with a normal structure. The microscopic structure of the cretinous thyroid has been worked out by Hanau and de Coulon. It shows an extreme atrophy of the epithelium, with thickening of the colloid. The thymus is often persistent.

Clinical Features.—Cretins are of low stature, usually from 1 to 1.5 meters (forty to sixty inches) in height when full grown, sometimes less, 89 cm. at twenty-two years, 91 cm. at thirty-seven years (Wagner). They are not smaller than other infants at birth. The body is short and broad, and that, with the low, broad forehead, flat nose with conspicuous nostrils, small eyes widely separated, the stolid expression, and muddy skin, suggests the Esquimo, but in the more severe cases the thick and blubbering lips, open mouth with large protruding tongue, add a semi-bestial aspect repulsive in the extreme.

The neck is short and thick; the thorax short, hollow, and in the female lacking in mammary development. The abdomen is large and pendulous. The legs are short, sometimes crooked, with small and weak muscles. The skin has characteristic changes; it is of chalky pallor, sometimes varied by brownish pigment, and is thick, inelastic, and cold; it looks œdematous, but does not pit on pressure. This myxœdematous condition sometimes disappears in the course of the disease. On the forehead the skin is wrinkled, and on the buttocks and genitals it is often in folds. The supraclavicular fossæ contain cushions, as in myxœdema; the submucosa of the mouth and pharynx is also sometimes thickened. The skin is usually dry and scaly. Sweating is scanty or absent. The hair is thin, coarse, and dry; scanty on the body; the beard does not grow. The nails are brittle, the teeth carious. The genitals remain undeveloped, as a rule, sometimes develop between the thirtieth and fiftieth years, but rarely to a stage making procreation possible. The body

temperature is low, the gait weak, waddling, or uncertain, sometimes limited to creeping.

Idiocy is an essential part of cretinism. It is parallel to the lack of development of the skeleton and genitals, assisted by deafness and anomalies of other special senses. In some cases deafness may be due to adenoid swellings in the pharynx. It, with lack of training, makes it difficult to test the degree of intelligence or lack of intelligence of a cretin. Sometimes only a few inarticulate sounds can be elicited. Individuals with less complete bodily and mental change are spoken of as "semi-cretins." Cretins are always apathetic, stupid, and lacking in memory and decision. They are not easily excited, but are sometimes vindictive. They can sometimes be trained to simple duties and become "hewers of wood and drawers of water." These, sometimes spoken of as "beast men," have about the mental development of a trained house dog (Kocher); others, less developed, are spoken of as "plant men." The vegetative functions are often good. The cretin is usually a great eater, but careless; he swallows food without chewing and easily overloads the stomach. The subjects of endemic cretinism sometimes reach fairly advanced age, fifty or sixty years.

Treatment.—The prophylaxis of endemic cretinism is a serious economic and social problem, like that of endemic goitre. Improvement of hygienic conditions and pure drinking water are essential factors. The treatment of individual cases may be carried out on the same lines as those given for sporadic cretinism. The improvement will depend chiefly upon the age, but even at ages when growth has in general ceased some improvement is possible. Growth and nutrition, including that of the skin, and also the intelligence, improve under thyroid medication, which must be kept up for years, probably for life. Wagner has seen good results from iodine treatment, and besides giving cretinous persons the benefit of sea air, as has long been proposed, it has been suggested that they be given iodine in minute doses, possibly in table salt, as Kocher recommends.

Sporadic Cretinism.—Synonyms.—Sporadic cretinism; congenital or infantile myxœdema; idiotie avec cachexie pachydermique; pachydermie crétinoide; idiotie crétinoide (French); infantile Myxidiotie (German).

Definition.—Sporadic cretinism is a disease nearly related to endemic cretinism and to myxœdema, but occurs where cretinism is not endemic, is characterized by imperfect development of the body and intellect, and is due to lack of thyroid secretion.

Etiology.—Thyroiditis from or in an infectious disease—such as measles, enteritis, or typhoid fever—or trauma, is probably one of the most important causes of sporadic cretinism. Tuberculosis, bad hygienic surroundings, alcoholism, and emotional shocks in the parents, especially at the time of procreation, or in pregnancy, are often mentioned in case histories. Infantile myxœdema sometimes occurs in two or more children of the same parents. Thyroid anomalies are not always possible to recognize. Paterson[1] reported a family in which two cases of myxœdema

[1] *Lancet*, 1897, ii, 849.

occurred. In the third pregnancy the mother took thyroid from the fourth month, and a normal child was born. MacIlwaine has reported the cases of mother and child.[1]

Pathology.—The pathological anatomy is essentially like that of endemic cretinism. The undeveloped bones can easily be demonstrated during life by skiagraphy and the stage of ossification determined. The thyroid is sometimes goitrous (7 out of 60 of Osler's cases[2]). In most cases it is atrophied, as Fagge pointed out. Usually there is widespread atrophy, with very few acini preserved. In some cases there are microscopic evidences of hyperplasia. In a case mentioned by Adami, with myxœdematous changes of the hands and some other parts, and with cancer of the pituitary, there was no change in the thyroid. In many cases the thyroid is so small that it is supposed to be absent, or is found only after careful search in serial sections, as in the case of a myxœdematous idiot reported by MacCallum and Fabyan.[3] The skin shows changes like those in myxœdema. MacCallum and Fabyan describe a peculiar condition of the fat in the subcutaneous tissue, occurring in fine droplets in the fat cells, instead of one large drop.

The thymus is often hyperplastic, sometimes aplastic or normal. In some cases the hypophysis has been found enlarged. The brain is small, and the ventricles contain an excess of fluid.

Symptoms.—The disease is frequently congenital, but the symptoms rarely show themselves, at least well enough to make recognition easy, until the second year. This is usually attributed to the protective action of the mother's thyroid secretion in the milk, or to milk diet. There is little or no bone growth, so that the infant bids fair to become a dwarf. The fontanelles remain open, but evidences of rickets are usually absent. The teeth do not appear, or do so very late, and are imperfect. The muscles are small and weak, the abdomen large and pendulous, with umbilical hernia, as a rule. The skin and mucous membranes are thick, the former either from fat or from the myxœdematous infiltration. The hair is coarse and grows poorly. There is anemia with leukopenia.

The thyroid is usually atrophied. The bony skeleton acquires the cretinous characteristics. In the early months nothing abnormal can be recognized in the skiagram. Later the absence of ossification of the epiphyses, especially in the phalanges, is evident. Mental and physical development both seem at a standstill. The infant does not smile at the usual age, nor does it begin to walk. The figure becomes more and more cretinoid.

Infantile myxœdema varies in its features according to the stage of development at which the loss of thyroid function makes itself felt. If it occurs after the first year the fontanelles are closed. The length of the body and the degree of ossification are in proportion to the age at which the disease began. In such cases previous rickets may have affected the bones so that the changes are not merely those of arrested ossification.

[1] *British Medical Journal*, 1902 , i, 1261.

[2] "Sporadic Cretinism in America," *Transactions of the Congress of American Physicians and Surgeons*, 1897, p. 169.

[3] *Johns Hopkins Hospital Bulletin;* September, 1907, xviii, 341.

PLATE XX

FIG. 1

FIG. 2

Sporadic Cretinism, aged 21 years. (Case of Dr. Hermon Sanderson.[1])

Fig. 1. Before treatment.

Fig. 2. After four months' treatment.

FIG. 3

FIG. 4

Sporadic Cretinism.

Fig. 3. Four years old, beginning of thyroid treatment.

Fig. 4. Five years old, thyroid treatment for one year.

[1] Sporadic Cretinism, with Report of Three Cases in One Family. *Michigan State Medical Journal*, April, 1906.

Besides the stunted growth, the parts of the body do not show normal proportions. The head is relatively large, the face broad, "full moon;" the eyes wide apart, the lids thick; the ears are large, of waxy appearance; the root of the nose is low, the nostrils broad and flattened ("bull-dog" or "pug" nose). The lips are thick, protruding, and usually open and cyanosed; the tongue large. The chin is short, but there is often a "double chin," below the jaws, on the short, thick neck. The teeth are often carious or imperfect, but the former varies much with the care of the mouth, the latter with the age at which the disease comes on. Salivation is usual. The head drops forward, the upper vertebræ are curved, with the convexity backward, the lumbar spine often having an opposite curve, increasing the protuberance of the abdomen. The abdomen has the "frog-belly" shape, and usually shows an umbilical hernia or pseudo-hernia, containing fat but no intestines. The pelvis is small. The penis and scrotum are usually small, the clitoris and labia often œdematous. The legs are short. The tibiæ are sometimes curved, even without rickets or in the absence of thyroid treatment. The epiphyses may be enlarged. The hands are clumsy, "spade-like," or resemble paws. The extremities are usually cyanotic. The skin is thick, leathery, or tough, yellow, wrinkled, and dry. Perspiration is usually but not invariably absent. The hair is sparse, coarse, and dry. The thyroid is usually impossible to feel, but may be present, even goitrous. There may be soft, fluctuating masses of fat above the clavicles, in the jugular fossæ or the axillæ, not always symmetrical. The temperature is subnormal; there is great susceptibility to cold. The blood shows distinct anemia, sometimes as low in hemoglobin as 50 to 60 per cent.; the red cells vary in size and shape; the leukocytes are not increased. The mental condition varies, according to the age and development at onset, from mild to severe idiocy. Myxœdema in childhood without idiocy has been described by Marfan and Guinon, Brissaud, and others. In most cases the idiocy is of moderate degree. Deafness, from adenoids, or from middle ear disease, is very common, and has an important part in the failure of mental development. The patient can learn easy sentences, can be trained to some extent, but is dull, or apathetic or stupid; slow and awkward of gait, and difficult or impossible to arouse to mental or physical exertion. Anger and severe depression sometimes occur. Some patients are vicious, almost all dirty, and more or less helpless. Chvostek's phenomenon is usually present. The appetite is usually good, but there is often a repugnance to meat. Constipation is the rule. The metabolism is low; the calcium assimilation may be as low as one-third the normal.

Varieties.—It is possible to subdivide cases of sporadic cretinism according to the stage of growth at which the loss of thyroid function became effective, both bodily and mental symptoms showing fairly constant relations, but the intermediate stages are so numerous that such a classification is only of general application.

We can distinguish, with Combé:[1] Congenital myxœdema, with complete arrest of physical (dwarfism, "nanism") and mental (idiocy)

[1] *Traité des maladies de l'enfance.* By Grancher, Comby, and Marfan, 1897.

development; early infantile myxœdema, occurring in the first year, with less marked dwarfing and some intelligence, amounting to imbecility or semi-idiocy; late infantile myxœdema, occurring in the second or third year, with small body and inferior intellect. To these can be added the incomplete (fruste) form of atrophic myxœdema, corresponding, for the age of the patient, to the mild myxœdema of adults.

Diagnosis.—If the disease is known to the physician by experience, mistakes can hardly occur with fairly typical cases, or with atypical ones if the course can be followed for a short time. Knowledge based only upon reading, with a study of portraits, should enable one to recognize the disease without great difficulty, but has often led to erroneous diagnoses. A thorough examination of the patient is essential, and in most cases a careful differential diagnosis is necessary to prevent error. Patients with severe infantile dystrophies have a strong resemblance in certain ways, and a hasty conclusion, based on the facies for example, should be avoided, much more one based on idiocy. It is useful to consider the chief causes of error, and to learn the differential diagnostic features in each case.

The possible causes of error are rickets, dwarfism, Mongolian idiocy, achondroplasia, congenital adiposity, diffuse scleroderma of the newborn, and hydrocephalus. In all of the four first mentioned there is lack of growth, most marked in myxœdema and achondroplasia, and especially abnormality of bone growth. Rickets is frequently assumed when myxœdema is present, on account of deformities of the bones.[1] In all stages the differences between the swollen epiphyses and irregular epiphyseal boundaries of rickets and the lack of ossification of myxœdema are easy to demonstrate by skiagrams. Dwarfism ("nanosomia" is etymologically less accurate than "microsomia"), or microsomia, includes two classes, the pure dwarfs (microsomia simplex), miniature but well-formed people, and the much less rare microsomia infantilis, or infantile dwarfs, sometimes called "type Lorain," following congenital or acquired disease. The combination of idiocy and infantile dwarfism is difficult to distinguish from myxœdema, but can be recognized by the absence of the characteristic skin changes and of the cretinoid facies, the occurrence of sweating and the difference in the bones. Ateleiosis of H. Gilford[2] cannot be mistaken for sporadic cretinism.

Mongolian idiocy is not admitted by many observers as an independent disease. Many English writers consider it sporadic cretinism; Bayon thinks its existence unproved. It requires confirmation, and the name should only be applied to congenital idiots in whom there is a Mongolian slant of the eyes, with epicanthus. In many cases reported there was restlessness instead of the apathy of the cretin. Although myxœdema patients may have epicanthus, the other features of the facies of the latter are absent in Mongolian idiocy. Achondroplasia (micromelia, fetal chondrodystrophy) may be mistaken for cretinism, as in the classic

[1] The ingenious claims of Hertoghe (*Die Rolle der Schilddrüse bei Stillstand . . . des Wachstums*, translated by Spiegelberg, Munich, 1900) for the identity of rickets and hypothyreosis are not admitted by other students of both diseases.

[2] *British Medical Journal*, 1904, ii, 914.

experience of Virchow. Its most striking feature is the shortening of the extremities, much more marked than occurs in sporadic cretinism and absent in rickets and Mongolian idiocy. The cold skin and low temperature of the cretinoid, often with a slow pulse, are important features in distinguishing sporadic cretinism from the other diseases. The spade-like or paw-like hands of the latter usually differ plainly from the beaded hand of rickets and the "trident" hand of achondroplasia. In all suspected cases the size and condition of the thyroid gland should be investigated. Practice in all kinds of subjects will make this part of the examination more certain. In doubtful cases a careful trial with a thyroid preparation should be made. Slight improvement may occur under the use of thyroid in some of the other conditions, but nothing like the specific changes in myxœdema. Congenital adiposity may be of thyroid origin, but must be distinguished from hypopituitarism (see before, p. 815). Diffuse scleroderma neonatorum may be distinguished by careful study. Myxœdematous subjects may have hydrocephalus, but the ordinary subject, with high, overhanging forehead, can readily be distinguished from the cretinoid by a full examination.[1]

Prognosis.—Infantile myxœdema, if not treated, has a slow but sure course. The older the patient grows, the more marked are the symptoms. Improvement does not occur, even temporarily. The duration of life is short, usually less than thirty years, although some patients live to thirty-five, forty, or even fifty. Death is usually due to intercurrent disease. The modification in course and prognosis under specific treatment will be described later.

Treatment.—The most important part of sporadic cretinism is the specific treatment, based on the experimental work of Schiff and Horsley.

Methods.—Grafting of thyroids, as proposed by Horsley and carried out by Bircher and others, is rarely used. The same may be said of feeding raw or cooked fresh thyroids, which are not always easy to procure and easily decompose. Liquid extracts, or more frequently powders of the dried glands, are used, glands from sheep being official. The official preparations are: Liquor thyroidei, B. P., freshly prepared, 100 minims represent one gland, dose 5 to 15 minims; Glandulæ thyroideæ siccæ, U. S. P., Thyroideum siccum, B. P., one part equals five of fresh gland; dose, 1 to 5 grains. These are, on the whole, satisfactory, but it must be borne in mind that even when carefully selected they do not always agree in the amount of active principle they contain. A method of standardizing is much needed and an attempt is now being made to have the preparation contain 0.2 per cent. of iodine.[2] Even if standardized it would probably be necessary in each case carefully to observe the effect of the remedy, and adapt the dosage to the individual. The usual beginning dose is one grain of the powder, once or even three times a day, increasing according to the indications or results. The latter are

[1] Useful differential diagnostic points with skiagrams are given by Siegert (*Jahrbuch für Kinderheilkunde*, Band liii, p. 447) and by Hermann (*Archives of Pediatrics*, 1905, xxii, 493).

[2] Seidell and Fenger, *Jour. Biol. Chem.*, 1912-13, xiii, 517, and Fenger, *ibid.*, vol. xiv, p. 397.

less marked in proportion to the duration of the disease. The effects appear within a few days, usually, but sometimes later. Loss of weight is one of the first signs, then a more natural condition of the skin, with return of secretion of the sweat and sebaceous glands. Cyanosis disappears, the pulse becomes natural, the movements livelier. Sleep is more natural; apathy and indolence lessen. The hair grows rapidly, and becomes fine and glossy; the blood returns to normal. The "natural impulses of growth, which were in abeyance in the thyroidless condition, are let loose" (John Thomson), even at an age when growth has usually ceased, and often equal 1 to 2 cm. a month. The body becomes more shapely. The teeth grow, and the second set are often large and well formed. The development of the mental faculties varies much in different cases. It is most marked in patients under ten years. Some children, under treatment, rapidly catch up with their fellows of the same age in their studies; others remain wholly or partly idiotic.

After the patient has made a definite improvement under the maximum dose, of about 25 grs. a day in some cases, the dose is greatly lessened, or stopped at intervals, until a fairly accurate dosage has been discovered. The temperature is a useful guide in some cases, the object being to keep it about normal. The possibility of thyroidism or of severe symptoms must always be borne in mind, viz., loss of appetite, nausea or vomiting, nervousness, insomnia, rapid emaciation, fever, tachycardia, increased nitrogen metabolism, and extreme restlessness. All patients with myxœdema are much more sensitive to thyroid medication than are normal subjects, children, however, less than adults. Marfan, Immerwohl, Bourneville, and others have observed severe symptoms and even death from ordinary doses. Siegert reports the death of a rickety child aged eighteen months from a five grain tablet. The thymus was filled with small hemorrhages. In cases of rapid growth under treatment, bow-legs and bending of the tibiæ, and scoliosis, sometimes occur, events indicating immediate diminution of the dose.

The general treatment is by no means to be neglected. Diet is an important matter, as shown by the changes for the worse in hypothyroid infants after weaning, and by the experiments of Breisacher. Meat is a poison to such persons. Milk, starches, green vegetables, fruit, and cream soups are useful. Fresh air, bathing, and all other elements of healthy life should be provided.

MYXŒDEMA.

Synonyms.—Spontaneous and operative myxœdema; cachexie pachydermique (Charcot, 1880); cachexia thyreoidea; cachexia thyreopriva seu strumipriva.

Definition.—Myxœdema is a chronic disease characterized by trophic disturbances of the skin and subcutaneous tissue and by cachexia and mental disturbances, due to loss of thyroid function.

Etiology.—The form of myxœdema most fully understood is that which sometimes follows operations on the thyroid. This was observed in one of the earliest cases of goitre enucleation (Sick, 1867, reported by Bruns

in 1888), and in many patients afterward, but not clearly recognized as a symptom complex until after the publications of the Reverdins and of Kocher.[1]

The most important symptoms are mental inertia or apathy and the changes in the skin. In persons who have not completed their growth, all the signs of sporadic cretinism are present. It comes on slowly, usually many months after the operation. It is most intense after complete extirpation of the thyroid in a young individual. There are many degrees of severity, and one form can pass into another. Even severe cases are capable of improvement if the thyroid tissue left behind hypertrophies. Extirpation of four-fifths of the gland is sometimes followed by symptoms, or if atrophy follows a less extensive operation, the same thing will happen. The removal of a lingual goitre may be followed by symptoms, if the other portion of the gland is small. When cachexia follows partial extirpation, the condition is usually mild. The celebrated case of von Eiselsberg shows that metastatic neoplasms from a thyroid tumor can lessen the severity of the symptoms. Myxœdema has been known (Czerny) to occur in case of rapidly growing goitre, and to be relieved by extirpation of one-half the gland (Neudörfer). There is a great difference in the proportion of cases of myxœdema following total extirpation, due partly to methods of operating, partly to thoroughness of search among patients. Kocher, by continued observation, found all but one affected, and in that one there was a recidive. The relation of the operation to the myxœdema is put beyond doubt by the large series of experiments on animals.

In non-operative cases of myxœdema the cause is often impossible to discover. Alcoholism, tuberculosis, acute infections, such as typhoid fever, influenza, pneumonia, cholera, and syphilis, have all been considered and probably justly. Although the relation of syphilis has been questioned, the observations of Koehler and of Pospelow and the effect of specific treatment seem to leave no doubt. Pel[2] has observed a family in which a syphilitic father had one son with myxœdema, another with acromegaly. In all these cases atrophy of the thyroid, following infection or inflammation, might easily occur. Some would add to the above list, gout, malnutrition, malaria, exhausting diseases, and all kinds of excesses on the part of the parents. Psychic shocks and the accidents in the sexual life of women (postpartum hemorrhages), also rapid childbearing, and the menopause, seem possible causes of myxœdema in the descendants, less obviously, functional nervous disease.

Myxœdema is a disease of adult life. Beginning with the age of fifteen years, an arbitrary line of division between cretinism and myxœdema, there is an increase up to forty-five, then a decrease. The average age in women is thirty-eight years; in men, forty-two. More than half the cases in women occur between forty and forty-five, and in males two-thirds

[1] See the conclusions of Ewald (*Nothnagel's spec. Path. u. Therap.*, Band xxii) and von Eiselsberg (*Deutsche Chirurgie*, Band xxxviii) regarding the question of priority, and the data in the latter and in Lardy's "Contribution à l'histoire de la cachexie thyreoprive."

[2] *Berl. klin. Woch.*, October 30, 1905.

of the cases occur between thirty-five and fifty. Women are more often affected, in the proportion of 7 to 1. Multipara are especially predisposed. Many cases occur among the well-to-do, or at least those not in the poorer classes.

Family predisposition is often recognizable. Myxœdema has been seen in sisters; it is not rarely associated, in the same family, with goitre or exophthalmic goitre. Simple goitre and exophthalmic goitre may precede myxœdema, or the symptoms of exophthalmic goitre may be combined with those of myxœdema as the function of the glands becomes gradually lost.

Myxœdema is rare in the tropics. It occurs chiefly in cold climates; it is common in England and Northern Europe, less so in North America, where Howard[1] found 100 cases reported up to 1905. It is more frequent than the reports indicate. Moffitt has collected 83 cases in California. In some parts of England it is so common as to be spoken of as endemic, but is rare in Derbyshire, the traditional home of goitre in England. Maxey and Berkeley[2] have shown the existence, previously denied, of myxœdema in negroes. It has been found in natives of British India.[3]

Pathology.—Myxœdema occurring before the completion of bone growth causes an arrest of ossification, as has been described under cretinism, but limited by the amount of incomplete bone in the body.

The increased thickness of the *skin*, the "solid œdema," was at first considered due to mucin (Ord, Charles, Horsley, etc.), of which some observers found fifty times as much as normal. The condition is now considered due partly to a tissue resembling granulation tissue, containing an increased number of fibrils and nuclei, partly to an infiltration with an amorphous material resembling mucus in the lymph spaces. A similar infiltration has been described in other organs. The cellular infiltration is most marked around the hair follicles, sebaceous glands, and sweat glands. It is not unusual for the thickening to disappear wholly or in part in the later stages of the disease, and the discrepancies of various investigators may be due to this fact.

The *thyroid gland* is almost always reduced in size to one-half or one-fourth the normal; Ponfick found one weighing 4.05 grams. In rare cases it is absent. There is no relation between the reduction of size and the severity of the symptoms. In some cases the gland is enlarged, but it is then always diseased. It is generally pale, tough, and fibrous. Microscopically it shows scattered areas of atrophy of the epithelium, increase of connective tissue, and degeneration of the arteries. If colloid is present it is likely to be altered in refraction and staining reactions. Ponfick saw periarterial hemorrhages.

The hypophysis has been found enlarged, or enlarged and degenerated (Boyce and Beadle, Ponfick, and many others). In one case, Ponfick

[1] *Journal of the American Medical Association*, 1907, xlviii, 1226.
[2] *American Journal of Insanity*, 1897–98, liv, 415.
[3] Smith, *Indian Medical Gazette*, 1905.

found the hypophysis completely atrophied.[1] The thyroid was also atrophied.

Symptoms.—These usually develop slowly, from weeks to years passing before the complete picture is produced. The first notable symptoms are sometimes mental, sometimes in the skin. There is in some cases a frequent or constant malaise, with lapses of memory and other psychic anomalies. In others the swelling of the eyelids, dryness and yellowness of the skin, solid œdema, or the gait may first attract attention.

The thickening of the *skin* is usually first noted in the face, especially the eyelids, or in the chin, cheeks, and neck. The appearance is such as to lead in many cases to a diagnosis of nephritis, but the swelling does not pit on pressure, although it feels much like œdematous tissue in some cases. In others it feels like thick but healthy panniculus, obviously out of place. The terms "solid" or "stagnant" œdema seem misleading. The tissue rarely feels like that occurring in long-standing œdema. The skin is sallow or even yellow in color. Over the malar prominences there are red or sometimes cyanotic areas. It is rough or scaly, often greatly thickened over the wrists, hands, and feet, and on the wrists and hands is often wrinkled so as to form a lozenge-shaped pattern, while the fine lines of the normal hands and fingers are more or less obliterated. Scleroderma has often been noted. The skin is dry, and neither exercise nor nervous excitement causes sensible perspiration. Largely from this the electric resistance of the skin is increased. The sebaceous secretion is often absent. Flat warts and pigmented nevi of various sizes and shapes tend to appear in various parts. The forehead is often wrinkled, the eyebrows elevated, in order to raise the heavy lids from the line of vision. The cheeks are flabby, the lips thick, the lower one often everted. The tongue is large and clumsy in its movements. The insides of the cheeks, the soft palate, and pharynx are often swollen and of yellowish color, the mucosa stiff and dense, making swallowing and talking difficult. The ears are swollen. The teeth are often carious, and pyorrhœa alveolaris is common, but both of these depend much upon the patient's habits, and even in otherwise severe cases the teeth and gums may be healthy. The mucous membrane of the nose is also thickened, yellowish, and gelatinous. Curtis[2] has called attention to the possibility of the nasal mucosa being the first seat of the peculiar infiltration. The abdomen is large, usually pendulous. The arms and legs are altered in shape in some cases, the legs looking œdematous, but not pitting on pressure. The hands are larger than before the disease began, the fingers thick and clumsy. The name "spade-hand" (Gull) is sometimes suggestive. The hair becomes dry, coarse, and brittle, and falls out rapidly. On the head this often affects the edges of the hairy scalp most, causing the "frontal band alopecia" of D. Walsh or the "cassowary neck." The hair of the eyebrows becomes sparse and harsh, adding to the peculiar appearance of the face. The hair on the body falls out. The nails are often coarse and brittle, with longitudinal or transverse ridges, but grow

[1] *Zeitsch. f. klin. Med.*, 1899, Band xxxviii.
[2] *Journal of the American Medical Association*, 1894, xxiii, 486.

with normal rapidity. All the skin anomalies are worse in cold seasons. Soft, gelatinous pads, like fat, appear above the clavicles, on the front of the neck, thorax, or abdomen, or on the genitals.

The symptoms on the part of the mind and nervous system are striking and important. Weakness or loss of memory is almost always complained of, and all the mental proceses are slow. Indecision is marked. The patient is often listless or sleepy, and may even act like an animal in winter sleep (Charcot). The disposition is often kind and considerate, slow to anger, but at times showing bursts of rage. Some patients are suspicious; some have agoraphobia. Hallucinations of sight and hearing sometimes occur, and there may be delusions of seeing small animals, usually not voluntarily admitted by patients on account of the fear of being suspected of alcoholism. Insanity may develop, but, as Starr early pointed out, differs from most forms of insanity.

FIG. 64

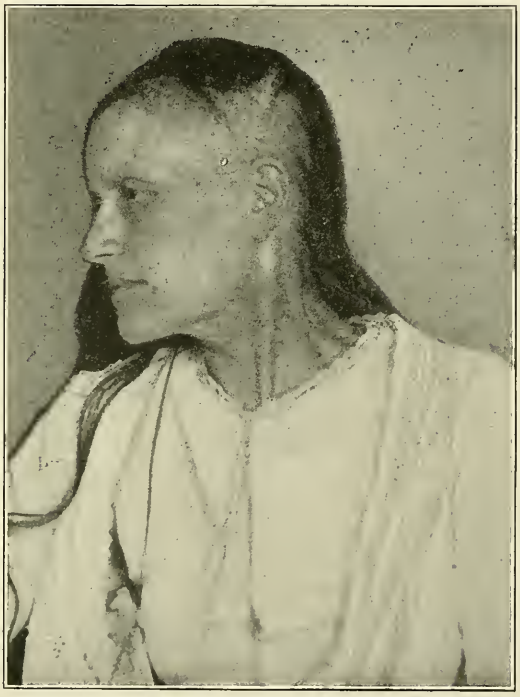
FIG. 65

Myxœdema. Original observation. Woman, aged fifty years. Hands showing changes under two months' treatment with thyroid extract.

Speech is usually slow, the voice often altered, muffled, or "leathery." The former is ascribed to a central, toxic affection, the latter to the changes in the tissues of the organs of articulation. Patients often show an unexpected garrulity, continuing to talk after the matter on hand has been settled. This may be related to the fact that they often leave the tongue out, after showing it, like patients in stupor. Not only is indolence marked, but any mental or physical exertion, such as reading or

housework, quickly becomes a burden. It is difficult to fix the attention, or to carry out a line of thought, but a certain degree of shrewdness may still be retained. The reflexes are weak and rarely absent. Cramps or spasms of the extremities occur; Chvostek's phenomenon can often be elicited. The gait is peculiar, usually weak and somewhat atactic, like that of a person stiff from overexertion. Patients often stumble and find especial difficulty in walking downstairs or on uneven ground. The chief reason for the gait seems to be the thickening of the subcutaneous tissue, perhaps assisted by alterations of the muscles. The head often has a tendency to fall forward or backward, even without drowsiness. Headache is frequent, sometimes suggesting that of nasal disease. Neuralgias and pains in the muscles, joints, and bones are not rare.

Fig. 66



Myxœdema. This shows the frontal band alopecia with new hair one-half inch long, the result of two months' treatment with thyroid extract.

The organs of special sense are often affected. The eyelids are swollen, often red at the edges. Use of the eyes causes weariness. Lacrimation is frequently present. Wagner has reported a case of neuroretinitis in which vision was much improved by thyroid treatment. Deafness is a common symptom, and depends usually upon myxœdematous thickening of the mucous membranes in the pharynx or ears. Tinnitus is frequent and troublesome. Taste is often absent, or there may be anomalies of taste, or a sensation of burning in the mouth, without evidences of

irritation. The swelling of the mucosa of the nose is a frequent source of irritation. Cleveland has called attention to swellings on the turbinate bones, of waxy pallor, improved by thyroid treatment.

The sense of touch is reduced where the skin is thickened. The patient is often painfully sensitive to cold, and all the symptoms are usually worse in cold weather. The skin is colder than in health, and the internal temperature is low, generally about 97° or 96° F., sometimes as low as 95° or 93° F.; 98° is to be looked upon in such cases as a febrile temperature.

The heart's action is weak, the second sounds sometimes accentuated. The pulse is infrequent, from 40 to 60 per minute, regular, usually of low tension. There is often arteriosclerosis beyond the degree to be expected from the patient's age. The heart may be dilated. Pain in the heart occurs even without thyroid medication. Hemorrhages sometimes occur in the skin and mucous membranes.

The blood shows more or less anemia in about half the cases, the red corpuscles being reduced to about 3,000,000, sometimes 2,000,000 or less per cmm. The hemoglobin is reduced to about the same proportion as the red cells; sometimes lower. Normal counts have been noted, and probably exist in cases with high specific gravity of the blood (A. Schneider). Kraepelin and Lebreton and Vaquez described increase in size of the red cells. Nucleated red corpuscles are not uncommon with low red counts. The leukocytes are usually not greatly increased, and show no noteworthy changes in their formula, unless an increased number of large mononuclear cells. Prout has noted large blood platelets.

Loss of appetite is very common, and digestion weak. Thirst is almost never felt. Constipation is often present, but diarrhœa, sometimes profuse and frequent, is not rare. Hemorrhoids are also likely to occur. The urine often shows no abnormality. The quantity is more often diminished than increased. The specific gravity is low. The nitrogen elimination is low. Albuminuria occurs in about one-fifth of all cases; in some of these cases other forms than serum albumin have been reported. Mucin has been found in considerable quantities under treatment. Nephritis, usually chronic interstitial, is comparatively frequent, but glycosuria is rare, and the carbohydrate tolerance is increased.

The mucosa of the labia often shows an infiltration like that in other mucous membranes. Leukorrhœa is often present. Menstruation is irregular in many cases. Bramwell[1] has reported the case of a patient, aged thirty-six years, myxœdematous from her twenty-fifth year, who menstruated regularly. Menorrhagia is sometimes marked. In one patient, judging from the history, it seemed to be the first symptom, soon followed by yellow skin, which was not unnaturally ascribed to the loss of blood. Sterility is frequent, but not uniform. Kirk reported a patient who had thirteen children during the disease. Improvement has often been observed in pregnancy. This has been ascribed to the influence of the fetal thyroid (!), but seems more easily explained by the increased nutrition in pregnancy. Hertoghe mentions spermatorrhœa as one of the results in the male.

[1] *Clinical Studies*, 1903–1904, ii, 329.

Many *varieties* of myxœdema can be recognized. Until recently it was supposed that there were two main groups, acute and chronic. The former we now recognize as tetany, but there are some cases of myxœdema that come on rapidly after operations, or in cases of goitre or exophthalmic goitre, or from unknown causes. Such cases were described by Ord, Charcot, and others. Among these may be placed Osler's remarkable case, reported to the American Neurological Association in 1898, in which a man, aged thirty-one years, had a rapid gain in weight, bloating of the face, enormous enlargement of the abdomen with splitting of the corium, diarrhœa, and irritable temper. Rapid pulse and bloody stools soon followed, with increased tachycardia, delirium, glycosuria, and death. Anders[1] has called attention to similar but less severe cases, suggesting a combination of myxœdema and Basedow's disease.

There are many varieties depending upon the completeness of the clinical picture. Many of these, in fact, are difficult to distinguish from certain cases of neurasthenia, psychasthenia, or senility, premature or otherwise. Hertoghe[2] is the most ingenious and thoroughgoing student of these cases, which have also been investigated by Pel, Buschan, Osborne, and others.

Myxœdéme fruste, larvate or incomplete myxœdema, is likely to be characterized by such symptoms as apathy, slight thickening of the subcutaneous tissue, flush in the malar regions, a sensation of or tendency to chilling, fatigue on slight exertion, mental or physical, anorexia, headache, pain in muscles, bones, or joints, obesity, asthma, eczema, psoriasis, urticaria, vomiting or diarrhœa, tachycardia, and a thyroid smaller than normal. It is well in all such cases to make a trial with thyroid preparations. Hertoghe would include among incomplete forms not only all infantile cases, but also such processes as adenoids, hypertrophies of the nasal mucosa, painful swellings of the liver, and varicose veins. It is certainly tempting to consider them, and many other changes, as due to hypothyroidism, and some are latent cases, but there are often contradictory features, and the therapeutic test is not always unequivocal. Another interesting variety is myxœdematous infantilism, a case of which was reported from the writer's clinic by Morris.[3]

According to the severity of the symptoms we can distinguish mild, severe, and intermediate cases of myxœdema. Murray has described a mild form in women aged forty to fifty years, which recovered spontaneously.

Diagnosis.—Myxœdema is easy to recognize if the symptoms are at all marked and the clinical picture borne in mind. The fact that cases are still occasionally mistaken for nephritis or jaundice shows the need of constant effort to avoid such errors by careful and thorough examination. Incomplete cases, and cases under the form of obesity, or lymphangitis, or trophœdema,[4] can only be recognized by careful examination, and usually prolonged observation under treatment.

[1] *Journal of the American Medical Association*, 1897, xxix, 63.
[2] *Nouvelle Iconographie de la Salpêtrière*, 1899, xii, 261.
[3] *International Clinics*, 1906, vol. iv, 17th series, p. 132.
[4] Meige, *Nouv. Icon. de la Salpêt.*, 1899, xii, 453; *ibid.*, 1901, xiv, No. 6; Parhon et Cazacou, *ibid.*, 1907, xx, 448.

Prognosis.—Before the thyroid treatment was known the outlook for the myxœdematous patient was hopeless. Progressive increase of symptoms, with relative improvement in summer and relapse in winter, usually brought the patient to a point in which any intercurrent disease proved fatal. Spontaneous recovery of distinct cases was rare, although Fraser reported one after ten years. The average duration was five to seven years. Under thyroid treatment the prospect is very different. In mild cases a practical cure can be obtained, and even in severe cases the symptoms can be so controlled that a symptomatic cure is possible under careful treatment. Death occurs from intercurrent disease, such as tuberculosis or pneumonia, or accident, like uremia or apoplexy, sometimes from severe intoxication, with nervous symptoms like those already described, and coma or prostration.

Treatment.—This may justly be looked upon as one of the most remarkable achievements of medicine. It is at present the best example of "substitution" therapy or organotherapy, better named opotherapy.

Methods of Thyroid Medication.—The usual method of treatment consists in the use of dried thyroid of the sheep, as mentioned before. Grafting[1] is still used, but has obvious disadvantages. Colloid of thyroid glands, tried by Cunningham (1898) and Buchanan (1899), is not at all promising. Iodothyrin has been tried by many, but is less effective than the dried gland. There is rarely any difficulty in getting patients to take the tablets, so that the rectal and inunction methods have no advantages. "Thyroidoerythism" of Poncet (1894), irritating the thyroid by means of iodoform plugs or foreign bodies, need only be mentioned as an example of the pains taken by some to avoid simple treatment.

The beginning *dose* is usually one tablet (2 grs. of dry powder) three times a day. Some patients cannot take this dose, but may begin with one tablet a day, or even less. Usually the larger dose can be taken, and increased up to five or six tablets daily, until a good result has been secured. The dose is then cut down, and the final amount determined by careful experiments.

The effect of the treatment is quickly evident, both on the physical and mental symptoms. There is rapid and marked loss of weight, greater in the early days of treatment and due to the loss of myxœdematous infiltration and of fat. The loss of weight may amount to twenty or thirty pounds, or more. The face becomes thinner, the eyelids lose their puffiness, and the eyes may even seem to recede into the orbital cavities. The malar flush disappears, and the cheeks take on a youthful pink. The fat pads disappear, the body and extremities shrink. Smaller gloves and shoes can be worn, and the stiff gait and inability to bend the body subside. The skin loses its harshness and dryness within a few days. Sweating returns and may be profuse and offensive. Menstruation reappears. Bramwell saw milk secretion in one case. The urine is increased in the first few days, but soon falls to the previous quantity. Talking and swallowing become easier. The memory improves, the mind becomes clearer, endurance and initiative return to normal. The hair

[1] Cristiani, *Semaine médicale*, 1904, No. 10.

begins to grow again, although the former hair continues to fall out. The hair has its natural color, even at advanced age.

The best results occur in cases with most swelling. As an example, in Kinnicut's case, the first one treated in the United States (1892), the woman had been ill for twelve years, was bedridden, deaf, and hairless, with intense mental and physical prostration. There was marvelous improvement within a few weeks; hearing became normal, hair grew down to the waist, the skin was of brilliant color and texture, and the patient, taking 5 grs. of fresh thyroid twice a week, was able to carry out important functions. Age is no obstacle to the result. Bramwell had a successful case at 69 years, after years of illness. The blood at first becomes more anemic, and then improves. Even growth of the skeleton may begin at ages beyond the usual period.

Important symptoms may occur during treatment, and must be carefully guarded against. F. C. Shattuck early pointed out the occurrence of cardiac pain with frequent pulse, elevation of temperature, and other symptoms. This has frequently been seen, and has led many to insist on the patient remaining in bed in the early weeks of treatment. If this is not done, the patient should be put to bed on the occurrence of any of the symptoms mentioned, the dose of thyroid cut down or stopped altogether, and ice-bags, strychnine, or cardiac stimulants used. At later periods such symptoms may occur even from small doses. Thus, Bonney observed exhaustion after 4 grs. Bramwell[1] saw distinct symptoms on taking one-half of a tablet, equal to $\frac{1}{128}$ of a gland. Putnam pointed out the occurrence of heart weakness long after thyroid treatment, and Murray saw a death from exertion, but, on the other hand, many patients become able to carry out considerable effort, as in mountain-climbing. Other toxic symptoms are: Delirium, somnolence, spasms, dyspnœa, albuminuria, glycosuria, pain in various parts of the body, erythema, or urticaria. Diarrhœa occurs in some cases, with or without nausea and vomiting. Thyroid extract is much more toxic to myxœdema patients than it is to healthy persons.

The skin usually quickly becomes healthy, but in some cases desquamation takes place in large areas, especially on the hands and feet. Foerster reported a chloasma-like eruption on the temples and forehead during treatment. He also saw abscesses form in the skin in places where camphor had been injected forty days previously. Œdema of the legs often follows the disappearance of the myxœdematous swelling.

In some cases there is a paradoxical condition. Larger doses of thyroid become necessary for the myxœdema symptoms, but the toxic phenomena are as severe as ever, as one of Ewald's patients observed. Atrophic cases are more prone to symptoms of depression, and these patients should be kept in bed in the beginning of treatment. Ewald recommends arsenic, in the form of Fowler's solution, three drops a day, as a preventive of symptoms of thyroidism.

During treatment, and after improvement has been obtained, the general condition should be carefully treated. The diet should be simple.

[1] *Clinical Studies*, 1903, ii, 261.

Meat should be excluded or reduced to the minimum; milk, vegetables, cereals, fish, and fruit are permitted. Alcohol is injurious. The patient should avoid severe cold, but should be in the open air as much as possible. Bathing and exercise must be adapted to the effects. Cold baths are never well borne.

THE PARATHYROID GLANDS.

Nomenclature.—Parathyroid glands; glandulæ parathyreoideæ (Latin); glandules parathyroidiennes (French); Beischilddrüsen (German); Ghiandole paratiroidee (Italian). Various other names have been proposed, such as Nebenschilddrüsen (Hofmeister, 1892), accessorische Schilddrüsen (Zielinska, 1894), glandules thymiques (Torneaux and Verdun, 1897), glandules branchiales (Verdun). Following A. Kohn's suggestion, many writers, especially in Germany, have used the term "epithelial bodies." While "parathyroid" is inconvenient in suggesting thyroid functional relations, it has the advantage of priority, and in English literature seems too well established to be changed. It is incorrect to apply the term "epithelial bodies" to the parathyroids specifically. Von Verebély's name, "branchial epithelial bodies," is more accurate, but awkward. The same criticism may be made of the terms "parathymus" and "parathyroid" for the two pairs of parathyroid glands. It would be better, perhaps, to follow Verdun's suggestion and speak of them as branchial glands (glandules branchiales) with the Roman numeral III or IV to signify the branchial cleft in which the gland originated and hence its position.

Historical.—The parathyroids were doubtless seen and partially described by earlier observers, notably Remak (1855) and Virchow (1863), but the first one to describe them specifically was the Swedish anatomist Sandström, who discovered one pair of these glands in 1880. Berger, who made a full abstract of the paper for *Schmidt's Jahrbücher,* should not be forgotten in this connection. Sandström thought the bodies were embryonic thyroid tissue in various stages of development, although he also recognized their resemblance to the pituitary body. Baber, Stieda, and Woelfler independently and about the same time described the bodies, but did not make clear their distinction from the interfollicular cells or undeveloped portions of the thyroid gland. Baber, in fact, spoke of the bodies as "undeveloped portions." Sandström left unsettled the possible physiological function of the bodies. He thought they might be important as the sources of morbid conditions in the neck, just as the accessory thyroid glands were.

Practically nothing was added to our knowledge of the bodies, nor were they often mentioned, until (1891) Gley rediscovered them, found they had been described by Sandström, and began a notable series of experiments to determine their function and their place in pathology. He, like Sandström, knew of only two parathyroids, the lower or "external" pair. Gley saw in them the explanation of the symptoms that sometimes follow thyroidectomy or strumectomy—the cachexia thyreopriva or strumipriva, characterized by myxœdematous or cretinous conditions, and tetany. By removing the thyroid with or

without the external parathyroid bodies he was able to produce or to avoid tetany. He therefore thought the parathyroids could compensate for the extirpated thyroid by differentiating into thyroid tissue. This belief was strengthened by finding, as he thought, hypertrophy in the parathyroids left in the body. These experiments, erroneous as the conclusions drawn from them were, had two important results. They gave an explanation for the difference in the results of thyroidectomy in carnivora and herbivora—the escape of the latter from fatal tetany being due to the greater ease of leaving undisturbed (two of) the parathyroids. Much more important, they stimulated numerous investigators to attack various problems relating to the parathyroids.

It was soon discovered (Cristiani, 1892 to 1893) that the parathyroids were sometimes embedded in the thyroid, and that some animals (bats, Nicholas, 1893) had four. Embryological studies by Prenant (1894) began to indicate the independent character of the bodies. This was made more certain by A. Kohn (1895), who showed that there were, as a rule, four parathyroids in various kinds of animals, distinguished between the accessory thyroid glands and the parathyroids, and identified these bodies with the "epithelial bodies" described by Maurer (1887) in amphibia. The advocates of the thyroid nature of the parathyroids continued to urge the older view, and their work had the beneficial effect of stimulating the other side to more careful and accurate experiments. Hofmeister proved that the bodies do not undergo compensatory hypertrophy after thyroidectomy. Such an enlargement, if it occurs, can be explained by the effects of the operation on the bodies themselves. Moussu (1897) asserted that thyroids and parathyroids have distinct functions, the loss of the former causing trophic disturbances, myxœdema, cachexia, or in young animals cretinism, the total extirpation of the parathyroids producing rapidly fatal convulsions. The partial loss of the parathyroids he thought caused symptoms suggesting Graves' disease. These ideas, especially the latter, continued to attract attention longer than they deserved, for it was shown by others that trophic disturbance also follow parathyroidectomy, and the relation to Graves' disease was shown, especially by MacCallum, to be unfounded both clinically and anatomically. Observations and experiments of Biedl, Leischner, Lusena, Christiani, Alquier, Welsh, and especially Vassale and Generali (1896), made it certain that there was a causal relation between extirpation of the parathyroids and the convulsive attacks well known to certain thyroid operators as postoperative tetany. It was known that tetany never followed the extirpation of a lingual thyroid; it was shown that the severity of tetany was in proportion to the amount of parathyroid removed, and that temporary tetany could be produced by interference with the blood supply of the parathyroids. "Tetania thyreopriva" became "tetania parathyropriva," with results speedily recognized by most surgeons. Jeandelize, Biedl, and Paltauf completed the demonstration of the difference between the chronic, trophic, thyroid symptoms and the acute, convulsive, parathyroid symptoms.

Physical Characteristics.—In size the parathyroids measure 3 to 15 mm. in length, 2 to 4 mm. in width and thickness. "They are flattened

and usually elliptical or tongue-shaped, and quite soft. This soft, flabby consistency aids greatly in distinguishing them from bits of thyroid tissue, which are much more firm and elastic, or from lymph glands, which are also much firmer. Their surface is always quite smooth and glistening, and except for the red lines of minute vessels, it is homogeneous in appearance, differing in that respect from the grayish pink or red lymph glands, in the surface of which the opaque lymph cords can generally be made out as whitish gray dots. In color they are of a clear light brown, which may be rendered pale by anemia and the accumulation of fat, or converted into a brownish red by congestion. It is particularly this bright brown color, together with their flabby softness, which makes them easily recognizable" (MacCallum).

Location.—The glands lie along the posterior inner edges of the lateral lobes of the thyroid, as a rule, but there are many variations. "It is often difficult or impossible to find both of them on each side; one or more may lie on the lateral aspect of the thyroid or even upon the part of the trachea below the thyroid as far as the bifurcation." "The recurrent laryngeal nerves, which have been suggested by certain surgeons as a guide to their position, run in a general way in the region where they are most commonly situated, but the glands bear no definite relation to them, and frequently lie far away from the line of their course."

MacCallum finds that the terms "inner," or "internal," and "outer," or "external," used with reference to the parathyroids in lower animals, are not so applicable in man as "upper" and "lower." "In most instances the lower and larger glands lie near the posterior edges of the thyroid lobes in the loose tissue which fills the notches just above the rounded lower lobules, and among the branches of the inferior thyroid arteries which enter the thyroid at those points. In most cases the upper glands lie against the œsophagus, at the points where the superior thyroid arteries fade away along the posterior edges of the thyroid lobes."

In man MacCallum did not find any of the glands embedded in the thyroid, as occurs commonly in the dog.

Accessory parathyroid glands occur and are frequent in animals. In a rabbit Erdheim found nine. The importance of such glands in anomalous cases need not be emphasized, but must be considered just as carefully as the probability of a smaller number than four, especially in cases demanding surgical operations with the possibility of removing or injuring one or more of the glands.

Embryology.—The parathyroids are generally believed to be derived from the epithelium in the third and fourth branchial clefts, very close to the lateral thyroid anlagen.

Structure.—The glands have a fibrous capsule which sends thin strands into the substance of the organs. The parenchyma is made up of epithelial cells with large nuclei, filling the meshes of the rich capillary network, and often arranged in branching beams. Along the stroma the cells are sometimes arranged in rows—"palisade" or "balcony cells." The cells were classified by Welsh as "principal" and "oxyphile" (acidophile, eosinophilous). The difference is probably due to various stages of functional activity. Glycogen and also fat granules are often

present in the cells, and have been considered products of parathyroid secretion.

From the time of Sandström various observers have noted clear spaces, cavities, or cysts, and sometimes a glistening fluid like colloid, although it is no longer believed that this is the same as thyroid colloid. Exchange between the cells and the blood is favored by the wide vessels lying with their endothelium directly on the cells. The capillaries are wide, of the type called "sinusoid" by Minot. Ginsburg (1908) has shown the existence of an anastomosis between the parathyroid arteries of the two sides. The parathyroid glands are ductless glands or blood-vascular glands of the most typical kind. They resemble many other small ductless glands, especially those now classed as epithelial bodies, including the epithelial part of the pituitary body, the cortex of the adrenals, and the islands of Langerhans. According to Kohn, the carotid gland and the coccygeal gland do not belong among the epithelial bodies.

Pathology.—In the case of the parathyroid glands, clinical and anatomical observations correspond closely with the results of experiments on lower animals. The most obvious and most remarkable effect of parathyroid insufficiency is tetany. First described by Weiss after strumectomy, in Billroth's clinic (1880), it was found to be the same as the condition known as tetany for many years before that. The experimental and operative phases, with full bibliography are well presented in the recent works of Biedl[1] and Guleke.[2] Postoperative tetany is now rarely seen, on account of improvements in technique. All mammals, birds, and tortoises are susceptible.

Following removal of two or more parathyroids, or their damage by ligature or otherwise, tetany usually comes on in from two to five days. In dogs it has been seen as early as seven hours after operation (Marine). In many cases the symptoms are severe, beginning with fibrillary tremors, rapidly passing on to tonic or sometimes clonic and epileptiform convulsions of the extremities, with "accoucher's hand." In the young there is spasm of the glottis. The breathing is rapid and labored; salivation occurs; stupor or coma develops, with death in a few days in severe cases. The temperature is not greatly elevated, the heart's action is sometimes accelerated but the blood pressure is usually not increased. All the special symptoms of tetany are present in such cases—Trousseau's, Erb's, Chvostek's and Hoffmann's, with irritability of the nerves of special sense and the sympathetic, as demonstrated by the reaction to adrenalin or pilocarpin. Irregular pulse, arterial spasm, angioneurotic œdema, spasms in the gastro-intestinal canal, leukocytosis, and disturbance of heat regulation may occur.

After incomplete extirpation, or temporary interference with the nutrition of the glands, there are milder symptoms, usually transient, called "tetanoid," or by Halsted[3] "subtetanic hypoparathyreosis." Sometimes the tetany is latent, the characteristic symptoms only coming

[1] Biedl, Artur, *Innere Sekretion*, 2, *neubearbeitete Auflage*, 1913.
[2] Guleke, N., *Chirurgie der Nebenschilddrüsen (Epithelkoerper)*, 1913.
[3] Halsted, *Amer. Jour. Med. Sci.*, 1907, cxxxiv, 1.

on weeks or months after the injury, and following some such cause as pregnancy, menstruation, trauma, infection or intoxication.

In non-operative tetany lesions of the parathyroids have been found, the observations being most numerous in infantile tetany,[1] with hemorrhage, but the attack may occur after healing of hemorrhage. Besides hemorrhage, other lesions, such as hypoplasia, cysts, tuberculosis, adenoma, carcinoma and leukemic infiltration, have been found in tetany. The same kinds of lesions have been found in cases in which tetany had not been observed, but latent tetany may easily be overlooked, and functional tissue may exist in sufficient amount to prevent tetany.

Besides the acute symptoms, in cases living some time, trophic lesions of great interest occur. The skin becomes eczematous, the hair rough, there is emaciation, and in young subjects changes in the bones resembling rickets and in the teeth loss of dentine, with pitting and transverse furrowing of the enamel. Conjunctivitis and a slowly developing cataract are not uncommon, and the liver and kidneys are the seats of degenerations.

In acute cases there is marked alteration of metabolism, which doubtless, in chronic cases, accounts for the emaciation. The chief anomalies are lowering of sugar tolerance; increased protein break-down which varies considerably, and increased excretion of ammonia, lime, and chlorides. Underhill and Blatherwick found in tetany disappearance of glycogen from the liver, and of sugar from the blood.

The pathology of tetany is still unknown. A single poison, tetany toxin, has been suggested, also a polyvalent antitoxin. The resemblance of tetany to ergot poisoning has been pointed out, and as B. imidazolylethylamin is the active principle of ergotoxin, and is also formed in the body from protein metabolism, the theory opens up interesting possibilities. Biedl thinks there is not an intoxication in the ordinary sense, but a "displacement of chemical coördination." MacCallum's early view that calcium deficiency excites the nerve centres is no longer held, but his suggestion that the seat of irritation is high up, perhaps subcortical, is recognized as probably correct.

The prognosis of tetany varies with its causes and the severity of symptoms.

The treatment, apart from prevention, is symptomatic or opotherapeutic. Transplantation has been successful in a number of cases, and in addition to postoperative cases, might be useful in some others, such as tetany in pregnancy. The best location for grafts is between the peritoneum and fascia. Grafts should not be taken from women, on account of the possibility of later pregnancy. Successful results have followed the implantation of parathyroids from recent cadavers, including those from infants (Pool, von Eiselsberg). Organic preparations, other than fresh parathyroids, have been disappointing. Thyroid preparations have apparently given good results, though the content of parathyroid, about one three-hundredth, seems too small to consider.

[1] See Escherich, Th., *Die Tetanie der Kinder*, 1909.

Calcium lactate should be given by mouth. The results are fleeting, but this is probably true of all treatment, including grafting, the main thing being to keep the patient alive until the accessory tissue hypertrophies sufficiently.

Other convulsive diseases have been thought to have parathyroid relations besides tetany, especially epilepsy (Jeandelize, Vassale), paralysis agitans (Berkeley), myoclonus, myotonia, and myasthenia (Lundborg). Erdheim, however, has thrown doubt upon the relation of epilepsy, as well as paralysis agitans. R. L. Thompson found the organs negative in nine cases of paralysis agitans. Eclampsia has also been thought to have some relation to the parathyroids, and some interesting observations have been made by Pepere and Zanfrognini, but their evidence is weakened by the contradictory findings of Erdheim.

R. L. Thompson has found degenerative or sclerotic processes in the parathyroids in primary infantile atrophy, such as are also found in the thymus and other glands. He does not emphasize the causal relation of the degenerations, but gives a laudable example of the kind of investigations needed. Atrophy has also been found in cases of pellagra (Mironesco), typhoid, pneumonia, congenital syphilis, and cancer of the pylorus.

A relation between parathyroid disease and osteomalacia and rickets has been assumed, but the anatomical evidences are contradictory. Erdheim found hyperplasia in 6 out of 8 cases. Schmorl found it once in 4 cases; Bauer in a mild case found adenoma. In osteitis deformans and senile osteoporosis (Todyo), and in a case of acromegaly (Erdheim) hyperplasia has been observed. Observations upon the organic metabolism in cases of parathyroidectomy show that the relations may not be very important, but the observations of Erdheim,[1] Stoeltzner,[2] Quest,[3] and MacCallum and Voegtlin[4] indicate that the mineral metabolism is very important. MacCallum's efforts to get a specific cytotoxin were unsuccessful. Gley, and also Mendel, found iodine in the parathyroid, but Estes and Cecil point out that the quantity is small.

An antagonism between the function of the thyroid and parathyroid glands has been assumed by some, and the experiments of Eppinger, Falta, and Rudinger suggest antagonistic effects of the two organs on the sympathetic nerves and the blood pressure raising functions of the adrenals. Lusena thought tetany was more severe in animals in which the parathyroids had been removed alone than in those in which the complete operation was done, and also that tetany after removal of the parathyroids alone was checked by subsequent removal of the thyroid. It seems more natural to explain this, if it occurs, as Vassale and Generali did, on the ground of lessened metabolism, and therefore lessened production of toxic material. MacCallum was not able to confirm Lusena's observations. Edmunds, and also Vassale and Generali,

[1] *Milth. a. d. Grenzgeb. der Med. u. Chir.*, 1906, Band xvi.
[2] *Jahr. f. Kinder.*, 1906, xiii.
[3] *Wien. klin. Woch.*, 1906, p. 830.
[4] *Johns Hopkins Hospital Bulletin*, 1908, p. 91, and *Proc. Path. Soc., Philadelphia*, 1908, Nos. 4 and 5.

found the thyroid colloid disappeared after parathyroidectomy. This might indicate increased functional activity.

A relation between the kidneys and the parathyroids has been supposed by some (Massaglia, Quadi, Manca). In MacCallum's case of parathyroid adenoma, cited below, there was renal insufficiency, "which had existed so long that extra demands might have been made upon the parathyroid." In two other cases of chronic nephritis MacCallum found signs of parathyroid activity in one but not in the other.

Tumors of the parathyroids have been observed, first by De Santi, later by Benjamins, Erdheim, Askanazy, Hulst, MacCallum, Weichselbaum, von Verebély, and J. Chalmers DaCosta. In several of these the change was apparently benign adenoma of moderate size, although in Benjamin's case the tumor was the size of a child's head. In Erdheim's case the mass was 2.5 by 1.5 cm. As no other parathyroids were found in the (autopsy) body, Erdheim thought the tumor had begun from the stimulus of a functional hypertrophy. In Hulst's case the tumor measured 2.5 by 2 cm.; in MacCallum's, 2 cm. Two normal parathyroids were found in the latter. MacCallum[1] found no colloid, as some others did. He suggests calling the growth adenoma, although recognizing that some so-called adenomata of glandular organs have proved to be compensatory or regenerative. The "parastruma" of Langhans sometimes contains colloid, in addition to the glycogen for which it is remarkable. Peripheral growth, penetration of bloodvessels and metastases assign it a place among malignant tumors. It is of great surgical importance.

Of other alterations that have been observed in the parathyroids may be mentioned cloudy swelling, cysts, fatty degeneration, "colloid" change, etc., as well as tuberculosis, but the cases reported are few, and the associated clinical features too insufficiently described to serve as guides to the normal or pathological functions of the glands. Certain so-called branchial cysts have interesting embryological relations with the parathyroids.

The use of parathyroid in conditions due to their insufficiency has been mentioned. Experiments with the administration of the glands in other diseases, such as myxœdema, paralysis agitans, Graves' disease, eclampsia, epilepsy, and psychoses, in the present state of our knowledge of the subject, are not strongly indicated. So far they have been disappointing.

[1] *Johns Hopkins Hospital Bulletin*, 1905, xvi, 87.

CHAPTER XXIV.

DISEASES OF THE THYMUS.

By ALDRED SCOTT WARTHIN, Ph.D., M.D.

General Considerations.—The thymus gland is originally an epithelial structure, arising as paired tubular epithelial diverticula from the dorsal portion of the pharyngeal aspect of the third visceral clefts. The two lobes of the gland are formed by the extension of these diverticula downward along the sides of the trachea toward the pericardium, expanding below to meet each other. The communication with the pharyngeal clefts is ultimately lost, while solid epithelial branches bud out from the expanded lower portion in a manner suggestive of a branched tubular gland. At the same time there is a subepithelial formation of lymphoid tissue which extends between and invades the epithelial portions of the organ until it finally becomes the most prominent histological feature. The epithelial elements become atrophic and undergo various retrograde changes, but their remnants persist in the form of the concentric corpuscles of Hassall, in some cases at least, if not in all, to the end of adult life. At birth the lymphoid character of the organ is so marked that it is usually classed with the lymph glands. The microscopic features of the gland are an investing fibrous capsule, connective-tissue trabeculæ, cortex of lymphoid tissue, and a medullary portion containing the Hassall's corpuscles and many eosinophile cells. Within apparently normal limits the weight of the thymus appears to vary greatly, and authorities differ widely in the standard of weight given. As usually given the weight ranges from 13 grams at birth to 26 to 37 grams at puberty. There can be but little doubt that the commonly accepted weights are too high. In common with Dudgeon, the writer believes that from birth up to the age of two years the average weight of the thymus is about 7 to 10 grams, and that glands, therefore, weighing 20 to 30 grams must be regarded as enlarged. The fullest development of the organ is reached at the end of two years. Atrophy of the lymphoid tissue, with its replacement by adipose and fibrous connective tissues, takes place gradually from the second year to the advent of puberty, and more rapidly after this time, so that in adults the thymus comes to be represented by a mass of fibrous tissue and fat, the so-called "thymic fat-body," containing small nodes of lymphoid tissue in which Hassall's corpuscles persist, even to extreme old age. A careful microscopic examination of the thymic fat of adults will show the presence of some thymic tissue, so that the common statement that the thymus is entirely absent in adults must be revised.

The anatomical status of the thymus cannot be said to be definitely fixed at the present time. Some writers would class it with the ductless

glands; others place it without question among the lymphoid organs. Basch may be taken as representing an extreme of the first view. He holds that the thymus is different from the lymph glands in all respects, embryologically, histologically, and chemically. He believes the "supposed" lymphocytes of the organ to be of epithelial origin and to retain their epithelial character. The opposite view is held, however, by an increasing number of writers. Maximow may be taken as a representative of this class. He holds that the lymphoid tissue of the thymus is truly lymphoid, and that it arises from histogenetic wandering cells developing in the mesenchyme from the endothelium and perithelium of the bloodvessels at a time when the thymus lobes show a pure epithelial character. The lymphoid cells wander in between the epithelium and change into typical large lymphocytes, increasing in number until the epithelial elements are thrown into the background. Finally, the organ comes to consist chiefly of masses of typical small lymphocytes, some erythroblasts, and myelocytes. The epithelium of the organ serves only as a favorable place for the development of the lymphoid tissue, as in the case of the tonsils. Indeed, the thymus may be regarded as a homologue of the latter. While we cannot at the present time absolutely deny a place to the thymus among the glands producing an internal secretion, the mass of evidence in favor of such a function is, when weighed without prejudice, very small indeed. And until the question is settled the best course to pursue seems to be to class the thymus with the lymphoid organs, inasmuch as the knowledge we do possess concerning its development and structure favors this view. Matsumaga has recently announced the discovery of lymphatic vessels in the thymus; his findings, however, are opposed by Schridde.

Of the *function* of the thymus we have as yet no definite knowledge. It has been assumed to be that of lymphoid tissue in general, and there can be no doubt that lymphocytes and eosinophile cells are formed in its lymphoid tissue. An erythropoietic function has not been shown to occur under normal conditions. We are wholly ignorant of the significance and function of the epithelial portion of the organ. Various writers have asserted that the thymus possesses certain vegetative functions, particularly in connection with the development of the bones, central nervous system, sexual apparatus, and the general metabolism of the body. With such hypotheses as a basis, numerous attempts have been made to establish the position of the thymus as an organ producing an internal secretion, and functional relationships have been assumed between it and the hypophysis, sexual glands, and the chromaffinic tissues. Whatever this hypothetical function may be, the majority of writers concede it to be only a temporary function in a certain phase of development of the body. Baumann demonstrated the presence of iodine in thymic tissue, and the investigations of Weintraud and Mayer have shown that thymus feeding causes a striking increase in the output of uric acid. Such an increase does not occur after thyroid feeding. According to Barry the amount of nucleinic acid is about five times as great in the thymus as in the lymph nodes. Schwarz and Lederer state that it contains an abundance of cholin. Thymectomy experiments in

animals have given contradictory results, but according to Thiroloix and Bernard, and Abelous and Billard, the removal of the thymus in rabbits and frogs gives rise to symptoms of intoxication proving fatal within a few weeks. When but half of the organ is removed death of the animal does not occur, but the remaining half of the gland becomes hypertrophic. Grimani and others deny that the removal of the thymus causes death in rabbits. Paton and Goodall were unable to make out any rachitogenic effects following extirpation, but Basch claims that the removal of the thymus in dogs causes an increased excretion of lime-salts and a deficient ossification ("experimental rachitis"). Complete thymectomy in children has apparently no effect upon the blood or nutrition, but König saw a florid rachitis develop in an infant whose thymus was removed when nine weeks old. According to Klose and Vogt the changes in the bones following thymectomy are due to an increase in the nucleinic acid content of the body from its non-synthesis when this organ is removed. They found in young dogs so treated that a peculiar form of obesity associated with cachexia developed "(idiotia thymipriva"), terminating in coma and death. They interpret this condition as a gradual intoxication by nucleinic acid. Bingel and Strauss believe that the thymus secretes a substance that lowers the blood-pressure. An inter-relationship between the functions of the thymus and spleen has also been assumed by some writers, but according to Paton and Goodall the simultaneous removal of thymus and spleen in guinea-pigs is without effect upon the nutrition, growth, development, and blood-formation of the animal. Injections of extracts of the thymus cause lowering of blood-pressure, cardiac weakness, dyspnœa, and finally death. Since similar effects may be produced by extracts of practically all other tissues, it is probable that the function of the thymus is not concerned with any direct action upon the vasomotor system.

Experimental work by Paton and Henderson apparently shows that there is a reciprocal action between the thymus and testes, each checking the growth of the other. Castration delays involution of the thymus, while removal of the thymus causes a more rapid development of the testes. Experiments in thymus grafting have, as a rule, been negative. According to Grimani the transplantation of the thymus does not lower the hemoglobin content of the blood, but is followed by a leukocytosis. The general nutrition suffers, but improvement follows the injection of thymus extract.

From the surface of the fresh thymus a thick fluid may be expressed. It is normally sterile, possesses an acid reaction, and consists chiefly of lymphocytes, with occasional eosinophiles, large hyaline cells, and polymorphonuclear leukocytes. This fluid has been regarded by some writers as representing the normal secretion of the gland, by others it has been interpreted as signifying various pathological changes. It is probably for the greater part the result of a postmortem change or digestion, as the fluid increases in amount in proportion to the time elapsing between death and autopsy. Ultimately the entire central portion of the thymic lobes may become liquefied. Inasmuch as such a postmortem softening or digestion does not occur in the lymphoid tissue in other

parts of the body, it may be assumed that there is some substance within the thymus responsible for this liquefaction (proteolytic enzymes).

The pathology of this organ has been strangely neglected during the past two decades, and with the exception of two conditions, atrophy and hypertrophy, but little has been added to our knowledge concerning its morbid states. The studies within recent years have, however, served to clear up some of the common misinterpretations of certain histological peculiarities of this interesting organ.

ANOMALIES OF THE THYMUS.

Total absence of the thymus has been reported, and an attempt has been made to show some relationship between this anomaly and hemophilia, general disturbances of development, infantilism, etc. Inasmuch as these observations were based upon the gross appearances alone, they cannot be accepted as wholly conclusive. A microscopic examination of the entire mass of fat and fibrous tissue would have to be carried out to establish the diagnosis of a complete absence of thymic tissue. In the case of true acephalic monsters the thymus may be entirely absent, and up to the present time such cases are the only ones in which a total absence of the organ has been definitely shown to exist. In acephalic, anencephalic, and hemicephalic monsters with developed thoracic cavities, the thymus may be smaller than normal or may be hyperplastic. In such cases the adrenals may be wholly absent or very small, and the hyperplasia of the thymus has been regarded as compensatory for the chromaffinic tissues. Hypoplasia of the thymus is also found in congenital myxœdema, and in association with hypoplasia of the testes.

Accessory thymic nodules may be found in the thyroid region and in the periphery of the thymic areas, and may present as subcutaneous tumors in the neck. They are to be regarded as persistent areas cut off from the main organ through the atrophy or non-development of the intervening portion. On microscopic examination, proof of their continuity with the main body of the thymus can often be found. Our pathological knowledge of accessory thymic tissue is practically nothing, but it is probable that some of the deep-seated primary cervical carcinomata of unknown origin may arise from such accessory thymic nodules. At least one case has been reported of an aberrant thymus undergoing hyperplasia and requiring surgical removal.

The cervical lobes of the thymus rarely extend to the level of the thyroid, but occasionally they may reach higher, even to the floor of the mouth. A third intermediate lobe is occasionally seen, sometimes extending downward toward the heart, in other cases, upward into the neck. The main lobes of the organ, both upper and lower, are often very tortuous and nodular, sometimes consisting of masses of thymic tissues strung together by narrow connecting cords or bands. Persistence of the original tubular structure of portions of the organ is not uncommon, giving rise to the appearance of gland tubules. These may be lined by simple columnar or ciliated epithelium. Thyroid tissue has been found in the thymus.

CIRCULATORY DISTURBANCES OF THE THYMUS.

Congestion.—The bloodvessels are involved in the case of any general circulatory disturbance, such as anemia or hyperemia. The thymic veins may become greatly distended in chronic passive hyperemia, particularly when due to cardiac lesions. As a result the thymus or the thymic fat may become much enlarged and reddened. Such a congestive enlargement may be mistaken at autopsy for a hyperplastic or persistent thymus, but it will usually be found during the progress of the autopsy that the enlargement disappears and the tissues become paler. It is also probable that the most severe thymic congestion may disappear at death and leave no trace at autopsy. Marked venous hyperemia of the thymus may be seen also in cases of asphyxia neonatorum, suffocation, pneumonia, diphtheria, etc., and possibly as the result of trauma. A careful differential diagnosis should be made in such cases from the hyperplastic thymus of the lymphatic constitution. As Dudgeon and others have pointed out, many cases diagnosed as "thymus death" are most probably due to "overlaying," but the coincident congestion of the thymus may have hastened suffocation. It must also be borne in mind that in the case of a hyperplastic thymus the acute increase in size due to an acute hyperemia has been regarded by a number of writers as the direct cause of thymic stridor and sudden death, the increase in size being considered sufficient to bring about a fatal result through pressure upon the trachea, neighboring vessels, and nerves. From recently reported cases there can be no doubt that congestion of the thymus alone, even when the gland is of normal dimensions or under these, may cause asthma or sudden death through pressure upon the structures lying beneath it. At autopsy the congestion may have entirely disappeared, and the gland present dimensions usually regarded as normal. An added clinical interest has been given to congestion of the thymus by its occurrence after goitre operations. Since thymic hyperplasia is frequently associated with goitre, both the simple and exophthalmic forms, such a postoperative congestion of the enlarged thymus may result fatally. Gluck has reported death following thyroid operations with symptoms of cyanosis, dyspnœa, and pulmonary œdema. Dwornitschenko explains these cases as the result of an arterial congestion of the thymus. After the ligation of the thyroid branches of the thyroid artery this vessel sends its blood into the rami thymici, causing an arterial congestion. The enlarged organ presses upon the vena anonyma and a secondary venous congestion is thus produced.

Marked *œdema* of the thymus may be seen in cases of universal œdema, and may cause pressure symptoms. It is also possible that acute œdema of the gland may occur, cause pressure symptoms, and entirely disappear at death. When large saline injections are given in the pectoral region just before death the tissues of the thymus areas and the anterior mediastinum may be found at autopsy to be markedly œdematous, and no pathological significance should be attached to such findings. Eosinophile cells are said to be absent in the thymus of cases of congenital heart lesions.

Hemorrhage.—The occurrence of small punctate hemorrhages in the thymus has been many times observed in newborn infants dying as the result of difficult labor, also in association with whooping-cough, empyema, bronchopneumonia, lobar pneumonia, asphyxia, suffocation, convulsions, hemophilia, purpura hemorrhagica, sepsis, status lymphaticus, epilepsy, etc. Dudgeon found hemorrhages in the substance of the thymus in about 95 per cent. of deaths from bronchopneumonia and lobar pneumonia. The small size of the extravasation deprives the condition of any clinical significance, but petechial hemorrhages in the pleura, pericardium and thymus are to be regarded as very important evidence of death from asphyxia. Friedleben alone has observed a larger "apoplexy" of the thymus occurring in the case of sudden death in a marasmic infant suffering from diarrhœa. The clinical and pathological significance of such a case it is at present impossible to determine.

RETROGRADE CHANGES.

The normal retrograde changes must be carefully distinguished from those representing pathological changes. After the second year the lymphoid areas become reduced in size and there is an invasion of the gland by fat and fibrous connective tissue. The cells of the lymphoid areas retain their lymphocyte character, although greatly diminished in numbers, while the reticulum is increased. Fatty degeneration of both lymphoid cells and corpuscles of Hassall is found in the majority of thymus glands without reference to the general condition of the individual. It may be confined to the periphery of the lobules or may be general. It occurs so constantly that it must be regarded as a normal process. In the case of pathological atrophy the lymphoid cells are replaced more or less completely by cells of the type of fibroblasts or endothelial cells. Calcification, cystic softening, etc., of the corpuscles of Hassall are also to be classed with the retrograde changes occurring normally. It may be noted in this connection that after the second year the weight of the thymus cannot be taken as a criterion of its condition, since an atrophic thymus may weigh as much as a normal one, owing to the great amount of fibrous tissue present. In the acute infections of childhood the cells of the thymic cortex often show slight degenerative changes, but the significance of these is not yet known.

Atrophy.—Pathological atrophy of the thymus must be regarded as one of the essential morbid conditions of this organ. Since we are as yet wholly ignorant of the nature and significance of these abnormal forms of thymic atrophy, we may, for the present, at least, follow Dudgeon in classing them as primary or secondary according to the absence or presence of other pathological conditions explaining the atrophy.

Primary Atrophy.—The association of thymic atrophy with a progressive and fatal marasmus in children has been pointed out by a number of observers (Ruhräh, Dudgeon, etc.). In many cases no definite cause for the marasmus can be ascertained. Improper feeding, imperfect assimilation of food, congenital syphilis, rachitis, toxemia of unknown source, etc., are among the etiological factors given. The autopsy

picture in these marasmic children is very striking. In addition to the marked wasting of the body or changes due to some terminal infection, the thymus is so reduced in size that it may easily be regarded as entirely absent. In the thymic area only a small mass of what appears to be œdematous connective tissue is found, which cuts with great resistance. The thick fluid seen normally is absent, and the lobular arrangement of the organ is not apparent. The weight of the entire thymic mass is usually about 2 grams. A fibrosis of more or less marked degree is present, the increase of connective tissue being diffuse and not limited to the interlobular portions of the gland ("sclerotic atrophy"). Fat cells may be either absent or present in the connective tissue. The arteries and veins may both show thickening of their walls. The cortex and medulla are not easily differentiated. The most striking histological change is the disappearance of the lymphoid cells and their replacement by cells of fibroblastic and endothelial type. Numerous giant cells resembling those found in the lymph glands in Hodgkin's disease may be present. The eosinophiles are apparently diminished. The corpuscles of Hassall are relatively increased; that is, they are brought so close together that they may form the chief feature of the parenchyma; they show the ordinary retrograde changes. In the case of terminal infection, hemorrhages may be present in the thymic substance. In addition to this the writer would call attention to similar changes occurring in the spleen and lymph glands suggesting a general lymphoid exhaustion. The primary atrophy differs from the normal involution of the thymus in that it is of the nature of a sclerosis without fat formation, while in the latter process there is a regular and uniform decrease in the parenchyma with the formation of fat tissue.

Secondary Atrophy.—Similar atrophic changes may be found in the thymus in cases of marked marasmus due to chronic tuberculosis, empyema, bronchiectasis, etc. Not all cases of secondary marasmus, however, are associated with marked thymic changes, while in primary marasmus the thymic atrophy appears to be constant. In the case of secondary atrophy the condition of the thymus might easily be explained as due to the existing chronic toxemia or malnutrition. In general it may be said that thymic atrophy is coincident with wasting of the tissues in children, and that the state of nutrition of a child may be judged by the condition of this organ. In the thymic atrophy due to starvation there is no fibrosis, but the weight of the gland is much reduced.

In so far as the clinical significance of atrophy is concerned, but little can be said at the present time. It is very doubtful if the so-called primary form is anything more than a local expression of some condition, intoxication or malnutrition, in which there is a general lymphoid exhaustion. There is no reason at present to believe that the thymic atrophy has any causal relation to the marasmus. It is very probable that a vicious circle between the associated disease and the damaged thymus is set up. The loss of thymic function must be sufficient to produce deleterious effects upon the organism as a whole. It might be worth while to try thymus feeding or the use of thymic extract in cases of obscure infantile marasmus.

There are no thoroughly satisfactory observations of the occurrence of *amyloid* in the thymus. *Hyalin* of the type of that found in connective tissue has been described as occurring in the corpuscles of Hassall, but such statements rest upon faulty staining technique. The hyaline change seen normally in the corpuscles is of the nature of cornification or epithelial hyalin. *Calcification* of the corpuscles is to be regarded as a normal event, and is not to be misinterpreted. It follows the hyaline change. *Cystic softening* of the corpuscles is to be similarly regarded. Pathological *pigmentation* has been recorded, but it is probable that the mediastinal lymph glands were the tissues involved.

ENLARGEMENT OF THE THYMUS.

Synonyms.—Persistence of the thymus, hyperplasia, hypertrophy, congestion, status lymphaticus, etc.

General Considerations.—Enlargement was the earliest recorded pathological condition of this gland, and is the one most frequently observed. In practical importance it overshadows all the other morbid states of this organ. Its relation to congenital and infantile stridor, asthma, and sudden death, either with or without a coincident enlargement of the lymph glands, has given to thymic enlargement a clinical interest not shared in by the other affections of this gland.

While it was early recognized that enlargement of the thymus might be the direct etiological factor in the conditions mentioned above, it was due largely to the dictum of Friedleben (1858) that the acceptance of this point was delayed for half a century and a controversy aroused over it that still wages to some extent. Numerous arguments have been advanced for and against the view that an enlarged thymus may cause stridor, asthma, or sudden death through pressure upon the trachea and the other important structures lying beneath the organ. Inasmuch as in the older cases the thymic condition was discovered only at autopsy, it has hitherto been impossible to formulate a scheme for differential diagnosis during life. In recent years an increasing number of such cases has been studied before death, and the possibility of an antemortem diagnosis has been demonstrated.

The chief symptoms of thymic enlargement are those of tracheal stenosis. About this point has centred the controversy of more than half a century, a number of writers denying that any enlargement of the gland could exert such a pressure upon the respiratory passage. Numerous cases have proved beyond all doubt that such a compression of the trachea does occur as the result of thymic enlargement, even when the increase in size does not far surpass limits ordinarily regarded as normal. Percussion, radiography, intubation, and operation in the living subject have established the clinical entity of this affection, while certain modifications in autopsy technique have increased the amount of postmortem evidence supporting it.

Etiology.—In a small number of cases thymic enlargement is due to congestion and œdema resulting from acute infections, general circulatory disturbances, or, more rarely, trauma. In the majority of cases the

enlargement is due to hyperplasia, and for this condition also it is very probable that there is a varied etiology. The primary cause may be sought in any infection, intoxication, or disturbance of metabolism in which there is a lymphoid or myeloid exhaustion. The enlargement of the thymus is, therefore, a secondary process of the nature of a compensation. In congenital syphilis and rachitis the thymic hyperplasia may with good reason be regarded as compensatory for the splenic fibrosis occurring in these diseases. In other cases we can only assume that the thymic enlargement is the result of some unknown lymphotoxic or myelotoxic condition. It is important to mention again in this connection the possible etiological relationship between adenoids and thymic hyperplasia. In the majority of cases thymic hyperplasia is associated with the lymphatic status. Likewise in exophthalmic goitre and Addison's disease, hyperplasia of the thymus is very frequent.

Pathology.—As the clinical manifestations of thymic enlargement are pressure symptoms, it becomes necessary to include under this head all enlargements of the thymus due to any cause (œdema, congestion, hyperplasia, new-growths, etc.). In the majority the enlargement is due to a hyperplasia of some one of the histological elements of the organ, but particularly of the lymphoid tissue. In a general way all thymic enlargements may be classed as *relative* or *absolute*. Under the first are included all those cases in which the thymus fails to undergo its normal involution, so that there is found in the adult body a thymus either of the same size as the infantile gland or smaller ("persistence" of the thymus). The term persistent thymus is not a good one, since it has been found that thymic tissue persists normally to late adult life, and undoubtedly many cases reported as persistent thymus fall into the normal class. It is better, therefore, to regard all cases in which the thymus retains its infantile size beyond the normal period of retrogression as instances of relative hyperplasia or hypertrophy. The etiology, clinical and pathological significance of such cases are the same as those of absolute hypertrophy.

As absolute hypertrophy may be classed all enlargements above normal limits, either before the period of involution begins (end of second year) or after this time. The cases of "persistent thymus" in which the gland is larger than normal would, therefore, be brought under this head. Since in the majority of cases the enlargement is due to a numerical increase of some one of the histological elements, the term hyperplasia is preferable to hypertrophy. In the remaining cases the enlargement is the result of congestion, œdema, or new-growth.

No definite proportion exists between the weight of the thymus and that of the body as a whole. If we accept seven grams as the average weight in the newborn, we must bear in mind that an atrophic thymus may be heavier, owing to fibrosis. Since there are so many conditions influencing the thymus weight, it would seem more expedient to base the diagnosis of thymic enlargement upon the dimensions of the organ rather than upon its weight. In general it may be said that any thymus weighing 15 grams or more is hyperplastic. By some writers 20 to 26 grams is put as the limit of normal weight. In the average case of enlargement the weight runs from 15 to 50 grams, but instances of

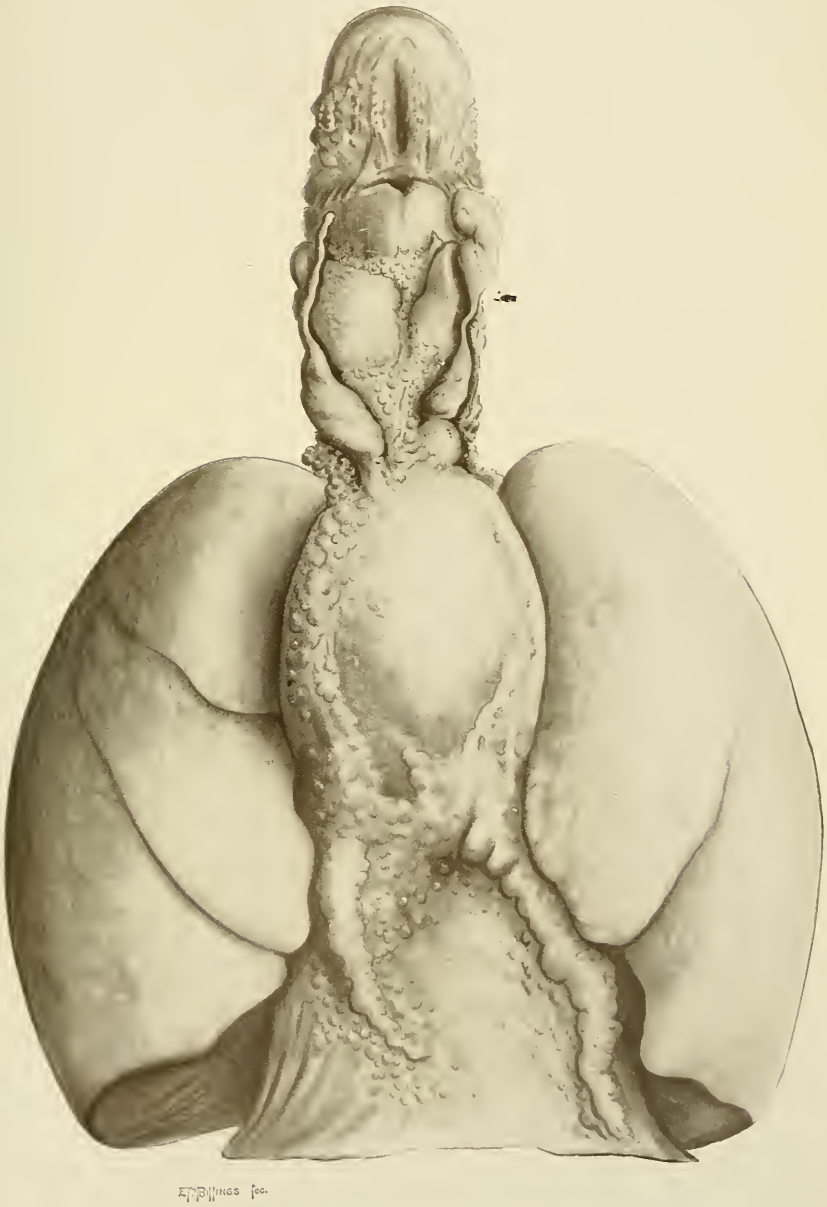
150 grams have been recorded. Such weights are probably associated with neoplasms rather than with simple hyperplasia. It must be emphasized that the postmortem size and weight of a thymus may be no index of its condition before death.

An increase in the thickness of the thymus is of far greater importance than an increase in any of the other dimensions. Grawitz, Pott, and others, have shown that the superior aperture of the thorax is a critical space, the trachea, œsophagus, great vessels, and thymus being contained within a space of about 2 cm. from the sternum to the vertebral column. In this space the thymus lies, applied directly against the anterior surface of the trachea. The sternum anteriorly and the vertebral column posteriorly form inflexible walls, so that an enlargement of the thymus to a thickness of $2\frac{1}{2}$, 3, 4 cm. or more must be provided for by a diminution of the space occupied by the compressible structures lying in it. Such compression of the trachea has been shown to exist by means of the tracheoscope, by the relief afforded by intubation with a long tube, and by the demonstration of flattening, atrophy, and anemia of the portion of the trachea lying in the superior thoracic strait.

As an argument against the possibility of compression of the trachea by an enlarged thymus gland, the statement of Scheele is frequently quoted. According to him, a weight of 750 to 1000 grams is necessary to compress the trachea of a child. Postmortem experiments of this kind cannot be taken as an argument in favor of the view that an enlarged thymus cannot exert pressure enough upon the trachea to cause compression, inasmuch as we are in total ignorance of the actual amount of intrathoracic pressure produced during life by an enlarged thymus. That the degree of diminution of the mediastinal space is the important factor, and not the weight or dimensions of the thymus, is evident.

That tracheal compression does result from thymic enlargement is definitely proved by numerous reported cases. Flügge found in 7 cases of sudden death in infants a marked compression of the lower portion of the trachea. Similar findings have been reported by other writers. On the other hand, such evidences of tracheal compression have not been observed in other cases of thymic enlargement, but this may be easily explained by the disappearance of the signs of compression after death. Biedert records a case in which the exploration of the trachea by a catheter through a tracheotomy wound showed the presence of a marked stenosis, while at autopsy the examination of the trachea after the removal of the enlarged thymus showed no evidences of such a compression. The trachea of the young child is very elastic, and resumes its normal form as soon as any pressure upon it is removed. Therefore, in order to demonstrate at autopsy any tracheal stenosis resulting from an enlarged thymus, the neck organs should be examined before the thymus is removed. Compression of the trachea by the enlarged thymus may also be demonstrated by fixing the neck and thorax of the child in formalin and alcohol before these regions are sectioned. These procedures should be carried out especially in medico-legal cases in which the cause of sudden death in infants or young children is sought. Hedinger has shown that a marked compression of the trachea may be demonstrated

PLATE XXI



Hyperplastic Thymus from a Case of Thymic Death in a Boy Aged Five-and-a-half Years.

(Patient of Dr. D. M. Cowie. Autopsy by the writer.)

by the above method in cases in which the size of the thymus does not exceed the limits of weight and dimensions usually regarded as normal.

Thymic enlargement occurs as an apparently independent condition, or with status lymphaticus, hyperplastic constitution, tonsillar hyperplasia, adenoids, rachitis, congenital struma, exophthalmic goitre, myxœdema, cretinism, acromegaly, myasthenia gravis, Addison's disease, epilepsy, congenital syphilis, scorbutus, leukemia, anemia, Hodgkin's disease, anencephaly, and the acute infections, or the enlargement of the gland may be due to a neoplasm. Excluding conditions such as leukemia, Hodgkin's disease, and lymphocytoma, in which the thymic enlargement is but a local manifestation of a disease process affecting all the blood-forming organs, there remains a group of cases constituting the great majority of thymic enlargements, and in these the thymus, on microscopic examination, is found presenting the appearances of a lymphoid hyperplasia. The acute enlargements occurring in association with the acute infections, particularly with diphtheria, etc., are due chiefly to congestion and œdema, but more or less lymphoid hyperplasia is usually associated.

The gross appearances of the hyperplastic thymus vary in different cases. As a rule, the main portion lies behind the upper part of the sternum, often extending more to the left of the median line than to the right, and downward over the upper third of the pericardium. The lower prolongations of the lobes may extend over the pericardium to the apex of the heart. The cervical prolongations of the lobes may also be hyperplastic. In a case of thymic stridor and sudden death occurring in a boy aged five years and a half, the hyperplastic cervical lobes extended to the floor of the mouth, the lower left lobe to the apex of the heart, the entire length being 18 cm. The main mass of the organ measured 7 x 5.5 x 4 cm. (See Plate XXI.)

The form of the hyperplastic thymus varies greatly. The anterior surface corresponds to the under side of the sternum and is usually convex; the posterior surface shows grooves and markings corresponding to the structures lying beneath. The hyperplastic lobes may be very nodular and tortuous. The color is usually pale pink or brownish red, the enlarged organ usually being paler than the normal thymus. On section the thymic tissue appears nearly homogenous; enlarged or cystic corpuscles of Hassall may appear throughout the cut surface as whitish or yellowish areas, in size about that of a pinhead or even larger. The consistency of the enlarged gland is usually softer than that of the normal thymus, and the postmortem softening of the central portion of the lobes is more marked and occurs more rapidly than in the normal thymus.

In the majority of cases the microscopic examination shows a lymphoid hyperplasia of the medulla, with or without congestion and œdema. The general structure resembles the normal. In other cases there is a marked hyperplasia of the medullary portion, while the cortex is hypoplastic. In my material a lymphoid hyperplasia of the cortex is often associated with a hyperplasia of the medulla, although Schridde states that in his experience a general hyperplasia of the cortical portion

never occurs alone, and that a general hyperplasia of both cortex and medulla is rare and found only in infants. The medullary hyperplasia is regarded by Schridde and others as the most important histological sign of status thymolymphaticus. The corpuscles of Hassall may appear more numerous and larger than in the normal gland. In patients older than two years the large size of the corpuscles forms one of the most striking microscopic features. In the glands showing passive congestion small hemorrhages may be present. The eosinophiles are usually increased and mononuclear eosinophiles may be present in large numbers. Smears from the cut surface may show the presence of myelocytes. Giant cells resembling those of the bone-marrow may also be present in the lymphoid tissue, particularly in the medullary portions about the trabeculæ and the corpuscles of Hassall.

The *spleen* and *lymph glands* may be either enlarged, of normal size, or atrophic. In each case the microscopic examination usually shows a lymphoid atrophy or exhaustion, with an absolute or relative increase in the stroma and a proliferation of the endothelial cells of the sinuses. The splenic follicles and the germ centres are reduced in number and size. The remaining ones may be made up chiefly of endothelioid cells. In the cases associated with congenital syphilis and rachitis the spleen often shows a marked fibrosis.

In the majority of cases of thymic hyperplasia the general pathological picture is that of the so-called "status lymphaticus," but the hyperplasia of the spleen and lymph nodes varies in degree. All of the lymph nodes may be hyperplastic or the hyperplasia may be confined to one or two glands. The bronchial, intestinal, mesenteric, and retroperitoneal nodes are most frequently affected. The rudimentary lymph nodes of the lungs, liver, etc., usually show a marked hyperplasia. The tonsils are nearly always enlarged and adenoids are usually present. But the significance of the status lymphaticus is that of the thymic hyperplasia which is present and is the cause of death (*status thymicolymphaticus*). No line of separation can be drawn between the occurrence of thymic hyperplasia as a separate condition and that associated with hyperplasia of the lymph nodes. The microscopic changes occurring in the spleen and lymph nodes in status lymphaticus are essentially the same as those found in thymic hyperplasia without hyperplasia of the lymph nodes or spleen. All transition stages exist between those cases with atrophic lymph nodes and those with enlarged ones. In the early stages the spleen and lymph nodes may show a lymphoid hyperplasia, but in the latter stages the condition of these organs is that of a lymphoid atrophy or exhaustion with hyperplasia of the stroma and endothelium.

Evidences of compression by the enlarged thymus may be found in the trachea. The great vessels beneath the thymus may be compressed and the heart may be hypertrophied and dilated. Marked dilatation of the left ventricle is almost always present in the thymicolymphatic cases, whether death be due to tracheal stenosis or cardiac paralysis. Compression of the right ventricle has been observed; and thrombosis of the internal jugular vein, due to the pressure of an enlarged thymus. Evidences of asphyxia are always present and the general picture is that

of death by suffocation. There is usually a marked infiltration of the peribronchial tissues, and this may be a cause of dyspnœa.

The body-fat is usually abundant and may be much increased. There is a more or less well-marked anemia. The facies is frequently of the adenoid type, and the complexion pasty. Thickening of the skin, with œdema and eczema, may also be present. In the majority of cases there are rachitic changes, and evidences of congenital syphilis may be present. Hypoplasia of the heart and aorta has been observed, as well as aplasia and hypoplasia of the chromaffinic tissues (Wiesel). In my own material the chromaffinic tissues showed no changes except in the cases of Addison's disease. The thyroid is often enlarged. Hypertrophy and œdema of the brain have also been described in cases of enlarged thymus. Anomalies of the sexual organs are not infrequent. In cases of persistent thymus retarded sexual development is often seen. A condition of infantilism may persist after the age of puberty.

Symptoms.—The essential symptom of thymic enlargement is a respiratory disturbance resulting from the diminution of space in the superior thoracic strait. This respiratory difficulty may manifest itself in all possible grades, from a mild stridor to a very severe dyspnœa with fatal termination. In general there may be distinguished three classes of cases, falling under the heads of *thymic stridor, thymic asthma,* and *thymic death.* As this classification is based upon the degree of severity, there is every possible transition stage, and the more severe forms may at any time develop out of the milder. Neverthless, this classification presents certain practical features, since some, perhaps many, cases never pass beyond the first or the second stage. Since the mechanical pathology of the condition has been demonstrated in so many cases, the term *thymic tracheostenosis* is preferable to thymic asthma and will probably replace the older designations.

Thymic Stridor.—In its mildest forms the chief symptom of thymic enlargement is a respiratory stridor resulting from tracheal compression. This is usually congenital or develops soon after birth. It is both inspiratory and expiratory, but is more pronounced during inspiration. The respiratory difficulty may be stationary or progressive, or the condition may manifest itself suddenly in its most marked form. In the latter case the attack may be precipitated by a prolonged fit of screaming or crying, particularly when the child's head is thrown backward. The stridor or the more severe asthmatic attacks may first appear during the course of some one of the acute infections, especially in connection with bronchitis, pneumonia, diphtheria, and whooping-cough. It is most probable that an acute congestion of the thymus lies at the foundation of these acute attacks and exacerbations. When the child is seen for the first time in such an acute attack, the diagnosis of diphtheria with laryngeal obstruction may be made and intubation or tracheotomy performed. No relief will be obtained from such procedures unless a tube long enough to pass the superior thoracic strait be introduced. The failure to obtain relief by such treatment should lead always to consideration of the possibility of thymic enlargement.

The thymic stridor is not accompanied by any modification of the

voice. When severe, there is an inspiratory retraction of the thorax, most marked in the scrobiculus and suprasternal space. In the mild cases such a retraction is not seen. There is never any hoarseness in the uncomplicated cases. In its mildest forms the stridor is simply an audible respiratory sound perceptible at a slight distance from the patient. The greatest intensity is usually at the end of inspiration, but rarely the stridor is more marked during expiration, and is then usually interrupted and vibratory in character, resembling the clucking of a hen, flapping of a sail, etc. A distinctly rattling sound may sometimes accompany the breath sounds.

The intensity of the stridor varies from the faintest audible breathing to a loud sound that may be heard at some distance from the patient. It persists during sleep, but is usually weaker. It is either not affected or is improved by a horizontal position. Occasionally the stridor disappears for several minutes without any apparent cause. Its intensity is increased when the child is excited or crying, but it may be somewhat weaker immediately after a fit of crying or coughing. In the more severe cases there may be a more or less well-marked dysphagia. Otherwise the child may appear perfectly well or he may present some one or all of the general symptoms mentioned below.

Thymic Asthma (Kopp's Asthma).—The condition of thymic stridor as described above is frequently progressive, and shows a marked tendency to exacerbations of an asthmatic character, or severe attacks of asthma may occur in a child showing no previous symptom of stridor. Kopp first described the condition as "*asthma thymicum.*" The condition may develop suddenly or follow the condition of stridor. The first attack may be fatal, or there may be periodical recurrences of progressive severity. Twenty to thirty attacks or even more may take place in the course of twenty-four hours. The child throws the head backward with a marked inspiratory stridor, the face becomes anxious and cyanotic, then pale, the pupils dilate, the extremities are extended, and the hands clenched. Spasmodic attempts at inspiration occur, and the picture presented is that of an impending suffocation. To the signs of tracheal stenosis there may now be added the signs of laryngeal spasm. There is an inspiratory aspiration of the glottis and a descent of the larynx. With the closure of the glottis the heart sounds become very weak, the pulse cannot be felt, reflex irritability is lost, and death may take place within two or three minutes.

Not all patients die, however. The attack may subside quickly, and the child may, within a short time, resume his play free from all symptoms. In other cases the severe dyspnœa passes away, but a marked stridor persists. A pronounced dysphagia is present also in these severe cases. Repeated attacks of greater or less severity may follow the first. Recovery may be permanent or temporary, but in a large percentage of cases the condition is progressive until terminating in death.

Thymic Death (Mors Thymica).—Between thymic asthma and thymic death no sharp line can be drawn, but the latter term has come to be applied particularly to those cases in which death occurs suddenly without a definite history of previous respiratory difficulty. The distinction

is based solely upon the degree of severity. In those cases in which the child is found dead, the phenomena of thymic asthma may have preceded death, and in the other cases it is very probable that a careful examination would have disclosed some evidences of tracheal obstruction. Nevertheless, in a proportion of cases an acute enlargement of the thymus due to a suddenly developing acute congestion brings on at once a laryngeal spasm or cardiac paralysis and the child dies immediately.

The great point of interest is the cause of thymic death, and around this has been waged the controversy concerning the part played by the enlarged thymus, this condition being the essential pathological feature. Kopp pointed out clearly the etiological relationship of this enlargement to sudden death, but Friedleben and his followers denied wholly that thymic enlargement had any pathological significance. Within recent years many writers have asserted the direct etiological relationship between thymic enlargement and sudden death, and the cases reported by a large number of careful observers leave no doubt that thymic enlargement is the direct cause of death. As to the exact manner in which it is brought about there is still some question. In many cases the symptoms and all the operative and postmortem evidence point to a suffocation resulting from tracheal stenosis and secondary laryngeal spasm as the chief if not the only cause of the fatal termination. To these may be added other effects of compression upon the heart, great vessels, vagi, and recurrent nerves. To a reflex spasm of the glottis may be added a reflex cardiac paralysis, or the latter may alone be the direct cause of death in those cases of sudden death in which all signs of tracheal compression or laryngeal stenosis are wanting: the so-called "*cardiac death*" ("Herztod"). A number of writers (Schridde, *et al*) concede that tracheal stenosis may be the mechanical cause of death in young children, but that in the status thymicolymphaticus cases death is usually *cardiac*. In my own experience the majority of cases of thymic death have been *mechanical*, but in a few instances I have been able to distinguish a *cardiac death*. In these marked dilatation of the heart was present, death was practically instantaneous without preceding stridor or dyspnœa, and the petechial hemorrhages of asphyxia were absent. This question can be settled only by a large number of careful autopsy studies. The direct action of the intoxication upon the heart or brain centres has also been regarded by some writers as a probable cause. The compression of the great vessels lying beneath the thymus may cause disturbances of blood-pressure, cardiac dilatation, thrombosis, etc. The increased intracranial pressure and the marked tendency to œdema, so characteristic of thymic enlargement, may be the results of such vascular compression, and the laryngeal spasm and cardiac paralysis may be but the immediate results of a sudden increase of pressure at the base of the brain. The marked pulmonary œdema seen in many cases of thymic enlargement may be explained as the result of pressure upon the pulmonary arteries or veins. An increasing number of reported cases reveal a pure mechanical pathology, *i. e.*, a thymic tracheostenosis sufficient in itself to explain all the clinical phenomena. Friedleben's dictum "Es giebt kein *Asthma Thymicum*" becomes a thing of the past.

We must conclude that the immediate cause and the manner of death vary in thymic enlargement, but the general picture is that of a convulsive attack of thymic asthma of the severest type. The muscular spasm suddenly ceases, the face becomes ashy, then intensely cyanotic, the lips and tongue swollen and livid, reflex irritability is lost, there is rapid cardiac failure, and death suddenly ensues. Attempts at artificial respiration are followed by the evacuation of urine and feces, but such efforts are without avail. The startlingly sudden character of thymic

Fig. 67

Case of hyperplasia of the thymus in a boy, aged five and a half years. Marked suprasternal prominence. Thymic asthma terminating in thymic death. (Patient of Dr. D. M. Cowie. Autopsy by the writer.)

death, when occurring in a child previously in good health, gives to it a unique atmosphere of tragedy that not infrequently leads to medico-legal complications. This is particularly the case when the child is found dead in bed, the suspicion of intentional suffocation not rarely being unjustly aroused. On the other hand, it cannot be doubted that the diagnosis of thymic death, or "status lymphaticus," has been carried too far, and that many cases of genuine "overlaying" have escaped under this convenient disguise.

The reported cases of thymic death tend to show that its occurrence is often apparently induced by a number of factors that have no effect upon the normal individual. Sudden death from fright or intense emotional excitement, during trivial surgical operations, anesthesia, while bathing, swimming, etc., has in many instances been found to be associated with an enlarged thymus gland. It is probable that a large proportion of the deaths occurring in surgical anesthesia are due to this condition. The fatal event may take place at any stage of anesthesia, from the first whiff to several hours after the patient has recovered from the effects of the anesthetic. The manner of death varies, in some being very sudden, while in others there is a slowly progressive cardiac or respiratory failure. Of my cases the only ones showing a "cardiac death" were those dying as a result of anesthesia.

An enlarged thymus has also been found in many of the sudden deaths associated with slight surgical operations, such as the extraction of a tooth, removal of adenoids or tonsils, injection of curative sera, etc. In some of these cases anesthesia was employed, and it is a question as to whether the anesthetic or the shock of the operation is responsible for the death. Thymic death has also been coincident with the use of external applications. In a case seen by the writer the fatal attack of thymic asthma was apparently induced by a slight burn of the skin from a hot-water bag. A large amount of evidence has been collected showing that cases of thymic enlargement are especially liable to sudden death while bathing or swimming. Many instances of sudden death from "cramps" while swimming have not shown the autopsy findings of drowning, but the presence of an enlarged thymus has been demonstrated. Cases of "found dead" in a bathtub also belong here, as well as those cases in which an accidental plunge into the water results in immediate death. Further, the occurrence of thymic death in the acute infections, particularly in diphtheria, is of great practical importance.

Relation to Status Lymphaticus.—It is evident that the condition of thymic death is that classed by many writers as the chief feature of the status lymphaticus. It is, however, a question as to whether the latter represents a definite primary pathological entity. It is much more probable that the clinical and pathological features usually regarded as characteristic of lymphatism consitute a cachectic complex secondary perhaps to a number of primary morbid processes, such as syphilis, rachitis, some latent infection, etc., that are characterized by an excessive demand upon the lymphoid and myeloid tissues. At a certain stage in the process the lymph nodes may be enlarged, and it is to this stage that the term status lymphaticus is usually applied. The examination of the enlarged nodes may show, however, the same condition of lymphoid exhaustion found in those cases of thymic death in which the nodes are small. The thymic enlargement is most probably to be regarded as a purely compensatory condition secondary to some primary lymphotoxic or myelotoxic process. Moreover, thymic enlargement leading to thymic death may exist without any of the other clinical features ascribed to the status lymphaticus. Nevertheless, the latter

term serves a very good function in designating the cachectic complex of thymic enlargement associated with adenoids, enlarged tonsils, rachitis, etc.

Physical Signs.—Inspection.—The general appearance may be that of perfect health, but in many cases the complexion is pale, pasty, or muddy. Persistent eczema is a common symptom. During the attacks of asthma there may be marked cyanosis. Evidences of a mild grade of rickets are seen in perhaps the majority of cases. During the asthmatic attacks there may be a pronounced retraction of the interspaces and scrobiculus. The upper part of the sternum may be prominent, or the enlarged thymus may present as a distinct tumor in the suprasternal fossa, usually being most noticeable during expiration. A bulging of the upper part of the sternum has been observed in a number of cases. During forced expiration a portion of the thymic tumor may be forced through the superior thoracic strait and present in the neck. A thymic tumor may present when the head is thrown back. Examination of the throat ordinarily reveals enlarged tonsils and adenoids.

Palpation.—The enlarged thymus may sometimes be palpated as an elastic soft tumor in the suprasternal fossa. The superficial lymph nodes may be more or less enlarged, and the spleen may be so large as to be felt below the edge of the ribs on deep inspiration.

Percussion.—The area of thymic dulness is triangular in shape, with unequal sides, the base at the level of the sternoclavicular articulation and the blunt apex above or behind the level of the third rib. The lateral boundaries extend somewhat beyond the sternal lines, usually somewhat more to the left than to the right. A small part of the thymus is covered by the anterior border of the left lung, but deeper percussion over this area will give a dull tone. On the right the area of relative dulness is very narrow, and is usually not taken into consideration. A thymus extending 2 cm. to the left of the median line will give on deep percussion an area of dulness extending 2 cm. to the left.

An area of dulness extending more than 1 cm. beyond the sternal lines may be taken as evidence of an enlarged thymus. In such cases the enlarged area may extend a little farther to one side than to the other, usually to the left. In children the thymic dulness is continuous below with that of the heart. In an adult with hypertrophic thymus the area of dulness may be continuous with the cardiac area, or may be separated from it by a zone of relative dulness or resonance of the width of an interspace or rib. In such cases the cardiac dulness is usually lower and farther to the left than normal. In Fig. 68 may be seen the area of an enlarged (persistent) thymus in an adult.

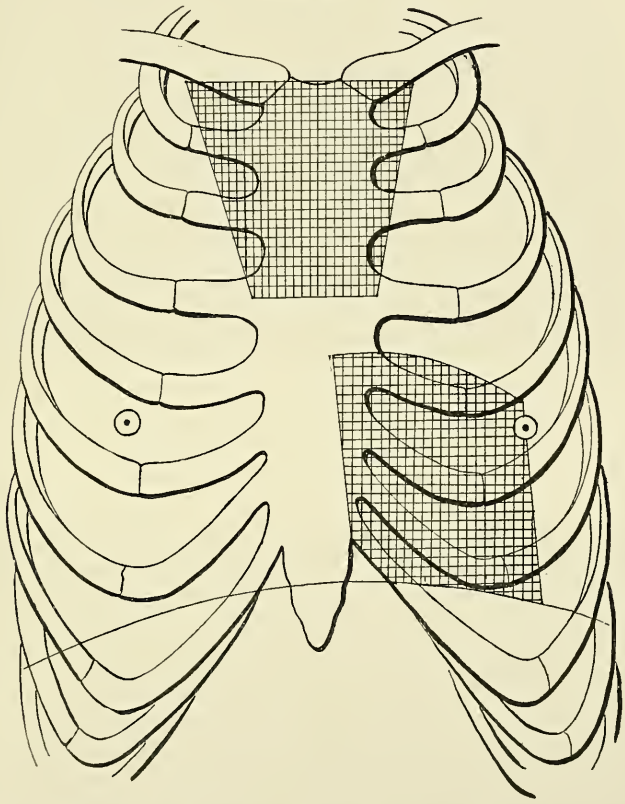
Boggs[1] gives a full description of the percussion signs of the enlarged thymus, and states that the thymic dulness can be made to shift when the head is thrown as far as possible backward, the lower border of dulness moving as much as an interspace or more. Jacobi also holds the view of a movable thymus dulness; Park and McGuire[2] criticise the views of Boggs and Jacobi as founded on a false anatomical hypothesis, the thymus being a fixed and not a movable organ.

[1] *Arch. Int. Med.*, 1911, viii, 659.

[2] *Ibid.*, 1912, x.

Percussion of the thymus from beneath while the child is held suspended face downward is also recommended, but this procedure is not necessary. In many normal children the thymic dulness disappears after the eighteenth month and sometimes even earlier. In general the area of thymic dulness may correspond to the area of dulness produced by tuberculous bronchial glands, as well as to that of aortic aneurism or mediastinal tumor.

Fig. 68



Percussion boundaries of "persistent" (relative hyperplasia) thymus in an adult.

Auscultation.—The most important auscultatory sign is the occurrence of an audible respiratory sound perceptible at a distance from the body, its greatest intensity being usually at the end of inspiration. When stronger during expiration, as occasionally happens, the stridor is interrupted and vibratory in character. It is heard distinctly all over the thorax, but is loudest over the upper part of the sternum. Its intensity varies greatly at different times. It persists during sleep and is not affected by a horizontal position. Occasionally it disappears for several minutes without any apparent cause. During the asthmatic attacks the stridor may be very intense. It is usually loudest when the child

is excited or crying, but may be somewhat weaker immediately after. The voice sounds are not affected. There is no hoarseness, although a clear barking cough is sometimes present. As a complication, the auscultatory signs of a bronchopneumonia may be added.

Radiography.—The radiographic examination offers the most certain method of diagnosis of thymic enlargement. Radiographs of apparently normal infants show some variation in the size of the thymus within rather narrow limits. In the median line of the thorax there may be seen a flask-shaped shadow having a narrow neck and a plump body, the neck of the flask reaching from the first or second dorsal vertebra to the fifth or sixth. The body of the flask corresponds to the cardiac shadow, while the neck portion, whose lateral boundaries only slightly exceed those of the vertebræ, is the shadow of the thymus and great vessels. The neck portion of the shadow gradually broadens below with concave lateral margins, and in children the thymic shadow is usually confluent below with the cardiac, but occasionally a clear or lighter zone may be seen between the two shadows. (See Plate XXII, Fig. 1.)

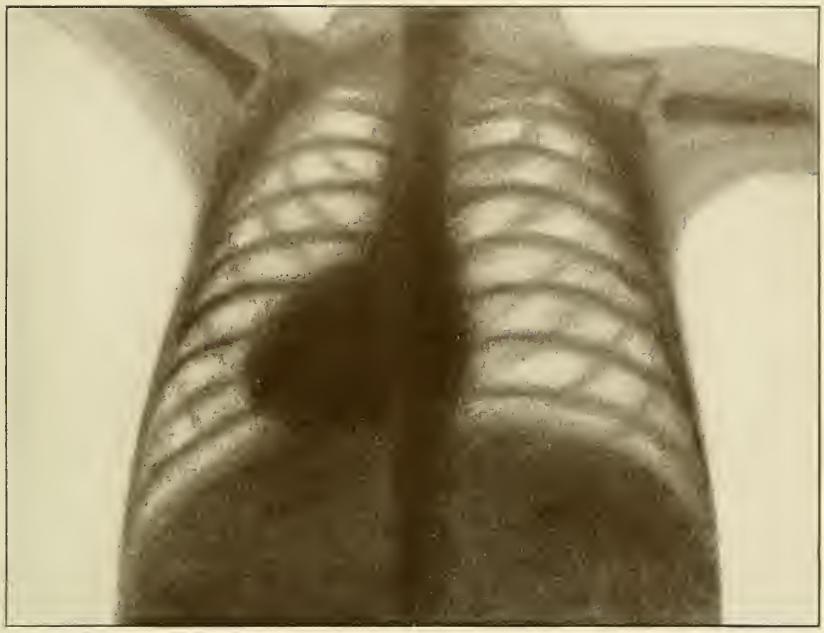
Under pathological conditions this median shadow is changed so that the neck becomes broader and confluent below with the cardiac shadow by convex lines instead of concave. (See Plate XXII, Fig. 2.) The enlargement of the thymic shadow is often greater upon one side, more often upon the left, and this agrees with the autopsy findings of asymmetrical enlargement. It must be borne in mind that an asymmetrical broadening of the thymic shadow may be produced by the child not lying flat. It should also be remembered that the shadows of heart and thymus are somewhat larger than the actual size of these organs. The radiogram gives no information concerning the thickness of the thymus. A very thick gland not increased in length or breadth may give a small shadow while severe symptoms of tracheal compression are present. On the other hand, an organ increased in breadth and giving an enlarged percussion area and a broad shadow may not be increased in thickness, and pressure symptoms may be wholly absent.

Local Examination of Respiratory Tract.—A laryngoscopic examination can rarely be made during the severe attacks of thymic dyspnœa. In the milder cases, when carried out, it is with negative results; no abnormality of the larynx is found. The stenosis of the trachea or bronchus may sometimes be seen by means of a tracheoscopic or bronchoscopic examination. In very doubtful cases these methods should be used when possible. A low tracheoscopic examination (tracheotomy) is safer than the attempt to make a high examination. Intubation of larynx and trachea in the usual manner reveals no laryngeal stenosis and causes no amelioration of the symptoms, but intubation with a tube long enough to reach the bifurcation may give instant relief and establish the diagnosis of tracheal obstruction.

General Symptoms.—The blood may show a more or less pronounced anemia and a relative lymphocytosis. Evidences of rachitis are present in many cases. The panniculus is usually abundant. Gastro-intestinal disturbances are not infrequent. There is a marked predisposition to catarrhal affections, tonsillitis, and adenoids. The general resistance

PLATE XXII

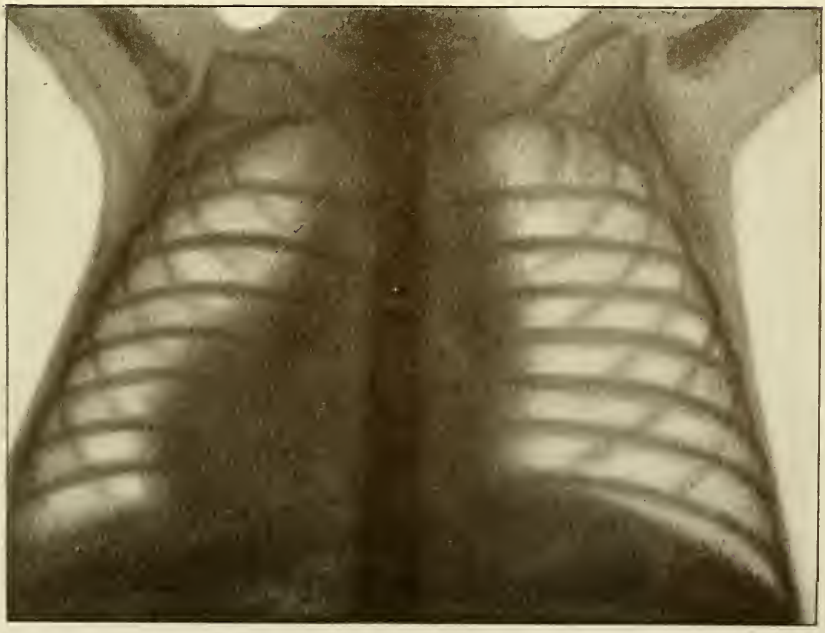
FIG. 1



Radiograph of Normal Child's Thorax.

Showing small thymic shadow with concave lines as it passes into the cardiac shadow.

FIG. 2



Radiograph of a Case of Hypertrophic Thymus with Stridor.

Large thymic shadow passing into the cardiac shadow by lines somewhat convex.

is weak. The circulation is poor and easily disturbed. A history of infantile eclampsia or idiopathic tetany is found in some cases, while in older patients attacks of dizziness and syncope are not uncommon. There appears also to be a definite association between thymic enlargement and epilepsy. The symptoms as a whole suggest a cachectic complex resulting from some intoxication or latent infection.

Diagnosis.—A congenital, chronic stridor, both inspiratory and expiratory, but most marked on inspiration, tending to exacerbations with the production of a dyspnœa so marked as to occasion intubation and tracheotomy and finally death, is usually due to thymic enlargement. The diagnosis may be easy when the thymus tumor can be made out by inspection, percussion, and *x*-rays. In case this cannot be done various difficulties attend the diagnosis. Similar symptoms may be caused through tracheal stenosis due to mediastinal abscess, tumor, aneurism, etc. Careful attention to all the physical signs will usually settle the question. Several other forms of stridor also occur in the newborn, and must be differentiated from that due to thymic enlargement.

The congenital stridor due to *malformation* of the vestibule of the larynx is purely inspiratory, the paroxysms are less grave and relieved by intubation with a short tube. The malformation may be determined by the examination of the larynx, and if it is not possible to do this with the laryngoscope the condition can be ascertained by a digital examination of the vestibule by one accustomed to intubation.

From the stridor caused by a *compression* of trachea or bronchi in the neighborhood of the bifurcation, as the result of pressure by enlarged or tuberculous lymph nodes, the thymic stridor can be distinguished by the fact that the former is purely expiratory, disappears during sleep, and diminishes when the child is inclined forward. It rarely appears before the fourth month, and as it is due to advanced tuberculosis of the bronchial glands in the majority of cases, it usually precedes death by a few days only. A number of writers call attention to the difficulty of distinguishing between thymic enlargement and diseases of the bronchial glands. When the stridor is congenital the thymus is usually the cause, but when it develops after whooping-cough or bronchopneumonia it is usually due to disease of the bronchial nodes. Boggs calls attention to the fact that the thymic dulness is higher and more superficial than that due to enlarged glands. The radiographic examination should be carried out in any doubtful case.

The stridor due to *adenoids* is distinguished by the difference in timbre and by its disappearance when the nostrils are closed, and the diagnosis may be readily determined by the examination of the nasopharynx. In the great majority of cases the symptoms, physical signs, and radiogram will establish the diagnosis beyond question. In rare cases without signs of tracheal stenosis the condition of thymic enlargement may exist without discovery until at autopsy, or even then may have subsided or disappeared so that the diagnosis fails entirely.

The *tracheostenosis* due to a spondylitic abscess may be distinguished with difficulty from that caused by an enlarged thymus. Hotz has reported a most interesting case of this kind, in which after the removal

of the thymus, the tracheostenosis persisted and caused the death of the child. Such a persistence of symptoms after thymectomy would, of course, point to other complications; but the removal of the thymus is justified by the relief given to the intrathoracic pressure. Temporary improvement may result until other measures can be carried out.

Prognosis.—In the present state of our knowledge it must be said that the prognosis in cases of thymic enlargement is in general grave. Since our conceptions, both clinical and pathological, are based almost wholly upon cases terminating fatally, we have no idea of the number of cases recovering. It is not at all improbable that many recover spontaneously. Those showing only the milder symptoms of stridor often recover after the second year, and recovery even from the more severe symptoms of tracheal stenosis has been observed. There is every reason to believe that with early diagnosis a fatal termination may be avoided in many, if not the great majority, of cases of thymic stridor and asthma. With intubation by a long tube offering immediate although temporary relief, and the possibility of a permanent cure through operation, the outlook is not so discouraging as it has been regarded. At the same time the prognosis in all cases of thymic enlargement becomes very grave in the case of intercurrent infections, operations requiring anesthesia, etc. A fatal termination often results from a slight bronchitis or common cold. Even the throwing of the head far back is sufficient to cause thymic enlargement and to set up a vicious circle that may lead quickly to suffocation.

Treatment.—This resolves itself along two lines: the prevention of thymic asthma and operative treatment in case the tracheal compression becomes so marked as to endanger life.

Preventive Measures.—Since the dangerous feature of thymic enlargement is suffocation resulting from the pressure of the enlarged gland upon the important structures lying beneath it, special care should be taken to avoid all conditions by which any increase in the volume of the gland might be produced.

1. *Position.*—A child having a large thymus should not be allowed to throw the head far backward. A high position of the head should be maintained, even if it is necessary to use special apparatus for this purpose. Some children do better when kept in a horizontal position, the stridor becoming worse when sitting.

2. *Avoidance of Excitement.*—Such children should be kept as quiet as possible. Attacks of crying or screaming, or of strong emotional excitement should be avoided. Excessive exercise, running, leaping, etc., should be prohibited.

3. *Operations.*—Surgical operations, especially those requiring anesthesia, are attended by unusual risks. Should such an operation be absolutely necessary, the situation should be fully explained to the parents and all preparations made for a possible tracheotomy and intubation of the lower portion of the trachea. Even with such preparations the suddenness with which thymic death may occur will in a certain proportion of cases render the precautions of no avail. The emotional excitement aroused by an attempt to make a laryngoscopic

examination may precipitate the fatal attack of asthma with spasm of the glottis and immediate death. Anesthetics must be administered with the greatest precautions. Tracheotomy should be done under infiltration anesthesia, and in the case of an operation upon the thymus, chloroform may be given through the tracheal cannula.

4. *Bathing.*—Very warm or cold baths are to be avoided. Thymic suffocation has been known to follow immediately the shock of immersion in hot and cold baths. Children or adults with enlarged thymus should not be allowed to go swimming or bathing.

5. *Prevention of Infection.*—Acute infections, particularly those involving the upper respiratory tract and causing thymic congestion are especially likely to excite attacks of thymic asthma that may end fatally. Unusual care should be exercised in the protection of children having large thymic glands from the possibility of acute infections.

6. *General Hygiene.*—This should be such as to increase the general metabolism of the body and its resistance to infection. The diet should be carefully regulated. Treatment for syphilis or rickets should be carried out if necessary, and particularly should attention be paid to the excretory organs. A quiet out-of-doors life in a good climate should be advised when possible. If the thymic enlargement is the result of a compensatory hyperplasia for an excessive drain upon the lymphoid tissues, the treatment should be that of general marasmus due to chronic intoxication or infection. Catarrhal affections of the upper respiratory tract, adenoids, enlarged tonsils, should be carefully treated.

Curative Treatment.—In those cases of thymic stridor or asthma in which there is marked dyspnœa with apparent danger of suffocation more radical treatment is demanded.

1. *Intubation.*—The introduction of a tube long enough to reach the bifurcation of the trachea may bring about immediate amelioration of the symptoms and save the child's life during a severe attack. Intubation with a short tube or the performance of tracheotomy is of no avail in thymic stenosis of the trachea. In the latter case the symptoms may be relieved by the introduction through the tracheotomy wound of a tube long enough to reach the bifurcation. The relief may be only temporary, as the symptoms of suffocation may follow the removal of the tube.

2. *Röntgen Irradiation.*—The selective action of Röntgen rays upon lymphoid tissues would indicate their employment in the hope of reducing the volume of the enlarged organ. There are certain considerations to be regarded as far as this form of treatment is concerned. The action of Röntgen rays in inhibiting further growth in the tissues of young animals exposed to their action, as well as the possibility of the production of an intoxication from the products of lymphoid disintegration must be borne in mind as possible dangers. For reasons based upon studies of the changes produced in the tissues by the Röntgen rays, their use in the treatment of enlargement of the thymus must be advised with caution. Recent writers affirm the successful employment of *x*-ray treatment of enlarged thymus and the lymphatic status, not only the thymus, but also the spleen and lymph nodes becoming smaller as the result of irradiation of the thymus alone, even when the spleen was

protected. The therapeutic value of the *x*-rays in thymicolymphatic status may be regarded as established, and irradiation is advised by some surgeons in preference to thymectomy.

3. *Antisyphilitic Treatment.*—If, as appears in some cases (Marfan's, Hochsinger's), the hyperplasia of the thymus is secondary to syphilitic fibrosis of the spleen, it might be well in all doubtful cases to carry out antisyphilitic treatment.

4. *Treatment for Rickets.*—The frequent association of rickets with enlarged thymus is sufficient reason for treating it in all doubtful cases.

5. *Operation.*—To the development of thymic surgery we must look for the most brilliant results in the treatment of hyperplasia of this organ. The pioneer work has been done, the possibility is proved, and the path pointed out. The experience of operators agrees as to the ease of the operation and its freedom from technical difficulties. As to the ligation of the thymic vessels, Ehrhardt compares the operation to the extirpation of a large mass of lymph nodes. Since in many cases the tracheal flattening is a chronic condition, there is some danger that the normal shape of the trachea lumen may not be resumed immediately after the removal of the thymus, hence Ehrhardt's precaution in keeping the wound open for several days is wise. The fact that so few operations upon the thymus have been performed may be explained by the rarity of diagnoses of enlarged thymus during life. There is, however, every reason to believe that with the development of thymic percussion and radiography an increased number of thymic enlargement should be diagnosed and operated upon, and the mortality of thymic enlargement and the status lymphaticus be correspondingly reduced. In the case of young children, resection of the thymus or stitching it to the sternum is advised rather than extirpation, bearing in mind the possibility of the effects of thymic function upon the development of the bones and sexual organs. Treatment with *x*-rays or partial removal of the organ are recommended rather than thymectomy in case of young children, because of the possibility of disturbances of development following the operation. In older individuals the organ may be completely removed without the danger of such after-effects. Klose also argues against thymectomy in young children, because of the danger of nucleinic acid intoxication.

General Treatment.—During the attacks of thymic asthma, hot or cold applications may be made to the neck and upper part of the sternum. Laxatives should be freely employed. Cardiac stimulants may be given when the asthmatic attacks are very severe. The threatened suffocation may also be averted by the use of oxygen. Still, all these measures are but temporary expedients, and unless relief is marked, intubation with a long tube should be carried out and the radical operation performed as soon as possible. Thymus feeding is apparently without effect upon the enlarged gland, but seems to have a general tonic action.

INFLAMMATION OF THE THYMUS.

Thymitis.—Acute inflammatory processes are apparently very rare, but thymic abscesses, either single or multiple, have been reported as

occurring in association with Ludwig's angina, pericarditis, pleuritis, pyemia, etc. Extreme caution is necessary in the diagnosis of thymic abscess at autopsy that no mistake be made in the interpretation of the thick, pus-like fluid found postmortem in the normal organ. It is very probable that the majority of the reported cases of thymic abscess are in reality based upon such misinterpretations. Especially is this probable when after the sudden death of a child the only pathological lesions found were small, single, or multiple thymic abscesses. There can be but little doubt that the so-called abscesses of Dubois are in the majority of cases the result of a postmortem softening of the medullary portion of the thymus, and in other cases the result of a proliferation and subsequent degeneration of lymphoid cells in the corpuscles of Hassall. Scridde describes them as proliferations of epithelial cells surrounding spaces filled with leukocytes, and regards them as syphilitic, having found great numbers of spirochetes in them. They must, therefore, be carefully differentiated from true thymic abscesses. A critical survey of the literature leads us to reject practically all cases reported under this head. The case reported by Pürkhauer of a four-year-old boy dying suddenly while in apparently perfect health, and showing at autopsy a thymic abscess that had ruptured into a bronchus, appears to be a true instance of thymic abscess.

Of acute or chronic non-suppurative forms of thymitis practically nothing is known. The fibroid changes described by Jacobi and others as analogous to the chronic interstitial inflammations of liver or kidneys may very well have been nothing more than the fibrous changes of primary or secondary thymic atrophy, and not inflammatory in origin. The cases of chronic thymitis reported in the older literature are all very doubtful, and probably represent a variety of conditions.

TUBERCULOSIS OF THE THYMUS.

Primary tuberculosis of the thymus is apparently of very rare occurrence, judging from the paucity of recorded observations. The majority are moreover, open to doubt, particularly those in the older literature. Care has not always been taken to differentiate the superior mediastinal lymph-glands from the thymus, and the latter organ has, no doubt, often been incorrectly included in the tuberculous mass arising primarily in these glands. Moreover, the same mistake has been made in this connection as with reference to the occurrence of gumma and abscess in the thymus, the physiological collections of thick fluid in the organ having been also misinterpreted as caseous tubercles. Although Pürkhauer and other older writers regarded the thymus as a frequent seat of the primary focus in general miliary tuberculosis of children, the recorded observations are unsatisfactory and inconclusive, and are for that reason rejected. The only observation of undoubted primary thymic tuberculosis appears to be the case reported by Demme. A child of non-tuberculous parents died in the third month of general marasmus, the only physical sign being some dulness over the manubrium sterni. The autopsy showed

an enlarged thymus gland containing several typical tubercles with tubercle bacilli. No other evidences of tuberculosis were found.

Secondary tuberculosis of the thymus is also rare, but a number of cases have been reported. Friedeleben found tubercles in the thymus in 3 of 73 cases of general tuberculosis, all being in early childhood. Jacobi saw three cases of secondary thymic tuberculosis in infants, associated with general tuberculosis. Pust has analyzed 12 cases of secondary tuberculosis of the thymus seen in the Pathological Institute at Kiel during the years 1875 to 1902, 3 of these cases being in adults. Dudgeon records 4 cases in which the thymus was involved. In addition, there is a small number of isolated observations of thymic tuberculosis associated with general or thoracic tuberculosis. No symptoms referable to the involvement of the thymus have as yet been recorded. In the case of large caseating masses replacing the thymus, dulness over the manubrium sterni would be found on percussion, and it is possible that pressure symptoms might be produced. A clinical differentiation between thymic tuberculosis and tuberculosis of the superior mediastinal glands would appear at present to be impossible. Moreover, a pathological diagnosis of thymic tuberculosis cannot be made positively without the demonstration of undoubted thymic elements in the tuberculous tissue.

SYPHILIS OF THE THYMUS.

Numerous statements occur in the literature concerning changes found in the thymus as the result of congenital syphilis. Hyperemia, hemorrhage, fibroid changes, thickening of the vessel walls, abscesses, cysts, etc., have all been ascribed to the action of syphilis upon this organ. It has even been affirmed by some writers that the thymus is the first organ to show the effects of congenital syphilitic infection, while others state that it may be the only organ in the body to show such changes. An analysis of the varied pathological conditions of the thymus ascribed to syphilis leaves practically nothing that can be said positively to be the direct result of congenital syphilis. As in the case of the "abscesses" described by Dubois, the majority of the supposed syphilitic conditions of this organ are nothing more than changes occurring constantly as a part of the normal retrogression of this organ, and may be seen in any thymus. Schridde (1912) describes "Dubois abscesses" containing great numbers of spirochetes, and therefore regards them as essentially syphilitic. I have found similar "abscesses" in the thymus in congenital syphilis, and am convinced that they represent gummata that quickly caseate and become softened. I find spirochetes in great numbers in the thymus, without recognizable histological changes, in the great majority of cases of congenital syphilis.

THYMUS IN OTHER DISEASES.

Acute Infections.—In children dying from acute infections the average weight of the thymus is found to be less than normal (Dudgeon). As the body weight is also diminished, a corresponding diminution in the

thymus weight would be expected. An exhaustion of the lymphocyte-forming tissue may also aid in bringing about such a loss of thymic substance. Congestion of the gland persisting after death will increase the weight and dimensions of the organ, but after the blood is out of the organ these fall below the normal. Careful studies of the part which the thymus plays in acute infections and intoxications are much needed, particularly with reference to the rôle of the lymphocytes and eosinophiles. Small hemorrhages throughout the tissue of the thymus are common in those cases of acute infection accompanied by lobar or bronchopneumonia. A marked passive congestion of the organ as a whole is constantly associated with these conditions. The other conditions described in the literature as occurring in connection with the infections, *viz.*, fibrosis, liquefaction, necrosis, degeneration of Hassall's corpuscles, etc., are for the greater part based upon misinterpretations of physiological or postmortem changes. In the latter class belong most probably the areas of karyorrhexis and necrobiosis described by Jacobi as occurring in the thymus in cases of diphtheria. Likewise, the observation made by Acland of peculiar changes found in the thymus in hemophilia and purpura is very doubtful.

Graves' Disease.—A relation between the thymus and thyroid has been affirmed by several writers. The fact that in this disease the thymus has usually been found to be persistent or hypertrophic has been taken as a basis for the assumption that there is some correlation of function between the two glands. The microscopic examination of the enlarged thymus found in cases of exophthalmic goitre shows no changes that can be regarded as essentially pathological beyond a simple hyperplasia. Enlargement of the thymus has also been observed in *myxœdema, myasthenia, Addison's disease, rachitis*, etc. Further, thymic hyperplasia has been noted as occurring in certain forms of *acromegaly* associated with enlargement of the hypophysis.

Cysts.—Through the retrogression of Hassall's corpuscles small cysts filled with a pus-like fluid (so-called "abscesses of Dubois") are formed in practically every thymus. They are usually of the size of a pea, but may be much larger. The cyst wall consists of a stratified, flattened epithelium, while the contents are made up of lymphoid cells that have either proliferated or migrated into the corpuscle and there undergo softening. These cysts have no relationship with syphilis or other pathological conditions. The larger areas of softening often seen in the centre of each thymic lobe have also been classed with the abscesses of Dubois. They are due to a postmortem softening or digestion of the lymphoid tissue. Definite cavities filled with a thick, yellow, pus-like fluid, often blood-stained, are thus formed. On microscopic examination the fluid is found to consist almost wholly of lymphocytes showing fatty droplets, karyorrhexis, etc.

Tumors.—Neoplasms arising primarily in the thymus are rare; and, further, many of the tumors reported as originating in this organ were most probably primary in the mediastinal lymph nodes. Positive proof of the primary thymic origin of a tumor lying in the superior part of the anterior mediastinum must be sought in the demonstration of the

presence of Hassall's corpuscles. In case the mediastinal lymph nodes are found not to be involved in any given case, it may be assumed that any tumor lying behind the upper portion of the sternum most probably arises from the thymus or its remains (Letulle's criterion). This, however, is not a very safe criterion, and the critical survey of all the cases reported as primary in the thymus leaves few that can be accepted.

Of the tumors reported as occurring in the thymus region, the most common form appears to belong to the group of closely related neoplasms embracing the *lymphoma, lymphadenoma,* and *lymphosarcoma.* Into this group fall also the tumor-like hyperplasias of the thymus seen in *pseudoleukemia* and *leukemia.* There can be little doubt of the close genetic relationship existing between such lymphoid tumors and the leukemias, and, following the plan adopted under tumor of the lymph nodes, the lymphoid tumors of the thymus may be divided into two classes, the *aleukemic* and the *leukemic lymphocytomas.* In the first class would fall the various forms of *round-cell sarcoma, lymphosarcoma, lymphoma,* and *lymphadenoma* without a coincident leukemic condition of the blood; into the second class, the *lymphoid tumors of the thymus associated with leukemia.* In leukemia the thymic tumor may be a secondary localization, or it is possible that there may be a primary thymic leukemia. Cases recently reported under the head of *leukemic thymus sarcoma* may represent this condition. The lymphoid tumors are usually the manifestations of a general disease, and are therefore malignant, hence their classification into benign (lymphoma, lymphadenoma, lymphocytoma) and malignant (lymphosarcoma), while based upon local histological characteristics of the tumors, gives a false conception of their nature. Not in every case of general aleukemic lymphadenosis is the thymus involved. It is also possible that myeloid tumors may be found in the thymus, with or without a coincident leukemia, but thymic myelosis is much less frequent than the lymphadenosis. It has been stated that the lymphoid tumors primary in the thymus form diffuse masses, while those primary in the mediastinal lymph nodes are nodular. In the late stages of Hodgkin's disease the thymus usually shows changes similar to those found in the lymph nodes, while in the earlier stages such changes are not present.

Medullary and *hemorrhagic round-cell sarcomas* have also been described as originating in the thymus, but are very doubtful. They probably belonged to the class mentioned above. The two cases of small round-cell sarcoma reported by Sheen, Griffiths and Scholberg[1] were undoubtedly lymphocytomas. The *lipomas* and *lipogenic sarcomas* in the upper anterior mediastinum are also of doubtful nature. The fatty tumors probably represent a local lipomatosis following thymic atrophy.

Primary carcinoma of the thymus has also been reported. Such an occurrence could be explained by the origin of the carcinoma from the epithelial elements of the organ or from included epithelial structures. *Secondary carcinoma* has also been reported, but some of these cases were undoubtedly metastases in the mediastinal lymph nodes.

[1] *Lancet,* 1911.

Teratomas and *dermoid cysts* of the thymus have also been recorded. The latter take their origin from epidermal inclusions or arise from bigeminal implantation, or from persistent epithelial anlage. The writer has seen a malignant teratoma of the thymus region containing multiple dermoid cysts, and giving rise to carcinomatous metastases.

Symptoms.—The symptoms of primary thymic tumor are in general the same as those belonging to the neoplasms of the anterior mediastinum. The sternum may be arched or eroded. On percussion an area of dulness over the manubrium may be made out. Pressure symptoms, such as stridor, asthma, cough, hoarseness, laryngeal spasm or paralysis, etc., may be present. The asthmatic attacks may end fatally. In the case of mediastinal dermoids the trachea or bronchus may be eroded and hairs may be expectorated. The radiogram may reveal a shadow.

Treatment.—Röntgen irradiation may be tried as a last resort. In the case of the lymphoid tumors the tumor may become greatly reduced in size. The only hope of a permanent cure lies in surgical operation.

THYMUS THERAPY.

Naturally the thymus would suggest itself as offering a proper field for experimental work along the lines of organotherapy, and many clinical investigations have already been carried out in this direction, but without as yet giving much hope of their being of any practical value. The administration of thymus gland has been carried out in exophthalmic goitre, simple goitre, myxœdema, acromegaly, Addison's disease, etc., and the results obtained are conflicting. Good results have been claimed in simple goitre and Graves' disease, but some of the most recent work with the latter disease tends to show that the treatment has no effect upon the goitre, heart, or exophthalmos, but appears to possess some value in improving the general condition. Good results have also been claimed for thymus feeding in rickets, and it might be well to try it in cases of thymic enlargement and status lymphaticus or infantile marasmus. On theoretical grounds, thymus feeding might be used in cases of precocious development. Fresh raw mutton thymus may be used, or tablets prepared from such; 10 to 25 grams are given daily. No ill effects have been observed in connection with such treatment.

CHAPTER XXV.

DISEASES OF THE SPLEEN.

By IRVING PHILLIPS LYON, M.D.

PHYSIOLOGY AND THEORIES OF THE FUNCTIONS OF THE SPLEEN.

Our present understanding of the normal and pathological functions of the spleen is fragmentary and confused. The spleen has long been an enigma and our present views are admittedly hypothetical and tentative. In view of the confusion, it seems advisable to summarize briefly the prevalent views and find what is really known and what is taken for granted or based on conjecture.

Nerve Supply.—The spleen is supplied by nerve fibres from the splanchnic nerves, through which a control of the size of the organ is maintained. Stimulation of the splanchnic nerves causes contraction of the organ, whereas cutting them causes splenic enlargement.

Movements.—The spleen is known to be abundantly supplied in its trabeculæ and walls with unstriated muscle fibres which rhythmically contract and expand at intervals of about one minute (Roy). These slight rhythmic movements are believed to assist in maintaining the circulation of the organ independently of the arterial blood pressure, in which respect the spleen seems to be unique among the organs of the body. In addition to these slight rhythmic movements, the spleen gradually enlarges during digestion, reaching its greatest size during the fifth hour and thereafter slowly returning to its former size by the twelfth hour (Dobson). This movement is probably a vasodilatation with a general relaxation of the musculature of the organ. The significance of this movement in relation to digestion is unknown.

Formation of Red Blood Corpuscles and Leukocytes.—Hematopoiesis.—The question whether in postuterine life the spleen ever reverts to its normal function of blood formation during fetal life has been much disputed and may be regarded as still unsettled, though the work of Meyer and Heineke, confirmed by Morris, greatly strengthens the assumption of such reversion in function. Meyer and Heineke,[1] in the histological examination of the spleen in 13 cases of severe anemia (pernicious anemia, 9 cases; anemia following sepsis, 2; anemia from cardiac disease, 1; leukanemia, 1), found evidence in every case of new blood formation, namely, collections of cells having the characteristics of myeloid tissue, consisting of nucleated red blood corpuscles (normoblasts), myelocytes, and "lymphocyte-like" cells, justifying them, they thought, in believing that the spleen had reverted to its fetal function of hema-

[1] *Verhandl. d. deutsch. path. Gesellschaft*, 1905, Band ix, 224; *Deutsch. Arch. f. klin. Med.*, 1907, Band lxxxviii, 435.

topoiesis. These observations have been confirmed by Morris,[1] in experimental pyrodin anemia in rabbits, who concluded that "the changes occurring in the liver and spleen in the experimental animals are similar histologically, so far as the hematogenetic cells are concerned, to those seen in the normal rabbit's embryo at certain stages in its development, and it may be assumed, therefore, that the spleen and liver have taken up their embryonic function, *i. e.*, hematopoiesis." Whatever the facts may be regarding the formation of red blood corpuscles, it is generally admitted that the spleen shares with the lymph tissue of the body in general in the formation of lymphocytes.

Destruction of Red Corpuscles.—Hemolysis.—The spleen has been regarded as especially concerned in the destruction of waste red blood corpuscles and leukocytes. This view is based on a number of facts, chiefly as follows: the presence in the spleen of a large percentage of iron in the form of an organic compound; the deposit in the spleen of quantities of blood pigment in various diseases accompanied by anemia; the presence in the spleen of large amœboid macrophages containing whole or partly disintegrated red corpuscles and leukocytes in conditions marked by great blood destruction; the evidence of vicarious or compensatory hemolysis in the new-formed hemolymph glands after splenectomy (Warthin), etc. These observations have led most pathologists to the opinion that the spleen is especially engaged in the function of hemolysis in pathological conditions, but the pure physiologists have not generally adopted this view. Thus, Howell (1913) concludes that the theory of the destruction of the red cells in the spleen cannot be considered at present as satisfactorily demonstrated.

Iron Metabolism.—The spleen contains a large percentage of iron in the form of an organic compound. After splenectomy there is a marked increase in the daily loss of iron from the body. These facts suggest that the spleen is concerned in a special degree in the metabolism of iron, possibly in the formation of red corpuscles, in the manufacture of hemoglobin, or in the conservation of the iron lost in blood destruction.

Protein Metabolism.—Enzymes.—The spleen has been believed to be actively engaged in nitrogenous metabolism and especially in the formation of uric acid. This has been assumed from the presence in the spleen of uric acid in considerable quantity, as well as other nitrogenous derivatives, such as leucin, tyrosin, taurin, xanthin, hypoxanthin, adenin, guanin, etc. The spleen has been found to contain an enzyme, adenase, which converts adenin into hypoxanthin (Jones, Schenck), but the significance of such a ferment, which at first seemed important in throwing light on the splenic function in protein metabolism, is apparently weakened by the finding by Schittenhelm, Lang, Burian, and others of the wide distribution of this and other closely related enzymes and their products in various organs of the body, viz., liver, spleen, pancreas, lungs, muscles, etc. Chittenden and Mendel[2] say: "A special influence on purin metabolism was at one time attributed to the spleen. Experiments by the writers have failed to substantiate such a view. In fact,

[1] *Johns Hopkins Hospital Bulletin*, June–July, 1907, vol. xviii, Nos. 195–196, p. 200.
[2] Osler's *Modern Medicine*, 1907, i, 711.

there is no evidence that the spleen exerts any special influence on either carbohydrate or proteid metabolism in general."

According to the work of Schiff, modified by the subsequent work of Herzen, Lepine, Gachet and Pachon, and others, the spleen has been represented as elaborating and furnishing to the blood a true internal secretion characterized by a definite enzyme which possesses a special affinity for the pancreas, the trypsinogen of which it activates and converts into trypsin. But it has not been established that such an action occurs normally, and in fact the general evidence is to the contrary, namely, that the pancreatic secretion does not contain free trypsin.

Relation to Infectious Diseases and Intoxications.—The relation of the spleen to infectious diseases and intoxications is not certain. In many such conditions the spleen is enlarged, congested, and may show acute inflammatory changes as well as sclerosis. Bacteria and protozoa and their toxins not alone produce such changes; as ricin, abrin, various coal-tar products, etc., may effect similar changes. We know little or nothing that is certain of the physiology of the spleen in such states, although it seems probable that it, in common with the lymphatic structure in general, shares in a defensive mechanism against microörganisms and their products, possibly in a special degree on account of the large amount of lymph tissue and its anatomical position in relation to the portal system. Splenectomized animals and human beings have not been found to show a permanent loss of resistance toward infectious diseases.

Action as a Reservoir for the Portal Blood.—The spleen is believed to act as a kind of safety valve or reservoir for the blood of the portal circulation, with which it is in intimate anatomical relation. This is suggested by its increase in size after digestion and its enlargement in diseases of the heart, liver, stomach, and intestines, attended with portal stasis. Such a mechanical function must be a very subordinate and insignificant one, shared in common, as it is, by the whole portal system.

Results of Splenectomy.—In the first place, all the facts prove that *the spleen is not an essential organ and can be extirpated without permanent detriment.* In general it may be said that the changes following the removal of the spleen for chronic disease are much less marked than those following removal of essentially healthy spleens for acute conditions, as, for instance, traumatic rupture. The difference seems to depend largely upon the establishment of compensatory changes for the lost splenic function. In the case of splenectomy in essentially healthy spleens the compensatory adjustment is pronounced, whereas in long-standing disease of the spleen such compensatory changes may be assumed to have previously developed so that further changes after splenectomy are less evident. The changes referred to are temporary enlargement of the lymph glands, development of new hemolymph glands, and changes in the blood, principally secondary anemia and pronounced leukocytosis. The glandular enlargement following splenectomy in man is exceptional, occurring in recognizable degree in only 3 out of 117 cases reported by Vulpius[1] in 1894; the blood changes are much more

[1] *Beiträge z. klin. Chir.*, 1894, Band xi.

usual although not constant. The anemia is generally moderate, unless much loss of blood has occurred at the operation, but the leukocytosis is usually pronounced with a tendency toward a lymphocytosis and a late eosinophilia. The blood changes appear early and continue over a variable period of months or years.

The results of experimental splenectomy on healthy animals have been, on the whole, greatly at variance and confusing. Perhaps the most fruitful and suggestive work is that of Warthin[1] on sheep and goats, whose conclusions were as follows:

"1. After total splenectomy in the sheep there is no evidence of regeneration of the primitive spleen or of the new formation of splenic tissue.

"2. The structural changes following splenectomy are: hyperplasia of existing lymphoid tissues, transformation of hemolymph nodes into ordinary lymphatic glands, and a new formation of hemolymph nodes out of lobules of fat tissue, and a later proliferation of the red marrow.

"3. There is no evidence of the formation of red blood cells in the lymph nodes after splenectomy.

"4. The function of hemolysis is taken up first by the hemolymph nodes, later by the ordinary lymphatic glands.

"5. The hemolytic function of the hemolymph nodes and hyperplastic lymph glands exceeds that of the primitive spleen, causing an excessive destruction of red cells. The resulting anemia is later compensated for by an increased activity on the part of the bone-marrow. It would appear, therefore, that the removal of the spleen leads to an increased production or retention of some hemolytic agent usually disposed of by the spleen. The effect of this agent is either to stimulate the phagocytes in the hemolymph nodes to increased activity, or to change the red cells so that they are more easily destroyed by these phagocytes.

"6. The presence of great numbers of eosinophiles in the glands, showing great destruction of red cells seems to point to some relationship between these cells and hemolysis."

Many other functions,[2] too numerous to consider in this place, have been ascribed to the spleen, but most of them are trivial or insufficiently supported by proved fact. We may conclude, then, in regard to the functions of the spleen, as Pawlow did regarding the bile, that "when a number of insignificant functions are assigned to any organ, it means that we do not know its real function or have not properly appreciated it."

MALFORMATIONS OF THE SPLEEN.

These are not infrequent and may be congenital or acquired as the result of disease or traumatism. Congenital malformations are chiefly of pathological interest, but their recognition may prove of practical value in the avoidance of diagnostic errors. They include the following types:

[1] Contributions to Medical Research, dedicated to Vaughan, June, 1903.

[2] For a fuller review of the theories of the function of the spleen, with references to 363 articles listed by title, see paper by A Meyer, *Centralbl. f. d. Grenzgeb. d. Med. u. Chir.*, 1914, No. 1, p. 41.

1. **Absence of the Spleen.**—Few cases are recorded, almost always combined with other anomalies of development.

2. **Small Spleens.**—Spleens, otherwise normal, weighing less than an ounce, have been observed.

3. **Large Spleens.**—Abnormally large spleens have been reported in infants at birth, generally in monsters. Very large spleens in infants and young children are usually instances of secondary enlargement due to syphilis, rickets, etc.

4. **Abnormalities of Shape.—Lobulated, Multiple, and Accessory Spleens.**—The spleen may vary greatly in form. The most common variation is found in the contour of the lower anterior edge, where the usual notch may be multiplied and exaggerated into deep indentations separating tongue-like or rounded processes projecting forward and downward. Such developmental anomalies must always be considered before assigning a pathological significance to extensions and irregularities of the free edge of the spleen. A remarkable abnormality has been recorded by Rolleston, the spleen giving off a narrow process, the thickness of the little finger, extending down the posterior abdominal wall into the left side of the scrotum, probably carried by the descent of the testis. Various furrows may penetrate the spleen in different directions, so marked, in certain instances, as to divide the organ into a lobulated structure, the so-called lobulated spleen. Multiple or supernumerary spleens are not rare, being found, according to Adami and Nichols, in 11 per cent. of all autopsies. They should be carefully distinguished from the common hemolymph nodes. The accessory organs may be single or multiple up to a large number. They are usually small bodies the size of a pea or bean, sometimes larger, and generally are either attached to the main spleen or lie close to it. Exceptionally, they are widely scattered in the abdominal cavity. Thus, in a remarkable case described by Albrecht, of Vienna, an enormous number of supernumerary spleens was found; in the usual situation there was a spleen the size of a walnut with the splenic artery and vein in their normal position; the other spleens were scattered not only in the mesogastrium but also on the peritoneum, as, for example, on the hepatic ligament and on the convexity of the liver; the largest number were found on the mesentery and transverse mesocolon; there were more than thirty in Douglas' pouch: each of these spleens was enclosed in a separate capsule covered by peritoneum and exhibited the structure of true splenic tissue.

5. **Malpositions.**—In association with other congenital defects the spleen may be placed in any part of the abdominal cavity or even, in case of diaphragmatic hernia, in the pleural cavity. In complete *situs transversus* the spleen and liver may be transposed.

MOVABLE SPLEEN.

Synonyms.—Floating spleen, wandering spleen, dislocated spleen, splenoptosis, splenectopia.

The normal mobility of the spleen is slight, depending upon movements of the diaphragm to which the spleen is attached by its suspensory liga-

ment. When this becomes permanently relaxed and elongated, the spleen becomes abnormally movable and dislocated downward, constituting the so-called wandering or floating spleen, which, according to the degree of elongation of the pedicle, may occupy any position in the abdominal cavity; it commonly occupies some part of the left side, but it has been found in the bony pelvis, on the right side, and even in the sac of an inguinal hernia.

Etiology.—The causes are those leading to relaxation of the splenic fixation, as dragging of a large, heavy spleen, pressure and traction exerted by neighboring organs, as an enlarged kidney, dilated and prolapsed stomach or colon, general enteroptosis, weakening of the normal support of the abdominal walls from repeated pregnancies or ascites, trauma, etc. The causes, in general, are similar to those producing movable kidney and general enteroptosis and, as in these conditions, are operative specially in the female sex; in fact, movable spleen is frequently only part of a general enteroptosis. Movable spleen is a distinctly rare condition, occurring in only 2 per cent. of cases of visceroptosis (Keith). Splenic enlargement, alone, must be considered as merely an exciting cause, as otherwise it would lead usually to dislocation, which is contrary to common observation; so also relaxation of the abdominal walls is only rarely associated with dislocated spleen, when the frequency of the former condition is considered. Another factor must be assumed, namely, an inherent weakness or predisposition to relaxation of the splenic ligaments, possibly a congenital defect, at least so in many cases, as also in enteroptosis and movable kidney; thus may be explained the occurrence of wandering spleen in several members of a family. Trauma alone may in rare instances be considered a sufficient cause.

Pathology.—This embraces both the primary morbid processes acting as etiological factors and the numerous changes depending upon circulatory disturbances in the displaced organ. The spleen may be of normal size in exceptional cases, although it is usually enlarged. The enlargement is not necessarily primary, as secondary enlargement may well be explained by disturbances of circulation leading to chronic congestion and hyperplasia. Rotation of the organ and torsion of the pedicle may occur and several twists of the pedicle are sometimes observed. Progressive splenic enlargement or sudden increase in size may follow strangulation of the pedicle, and even acute necrosis may result; on the other hand, chronic sclerosis, partial or general, with atrophy, may follow. Perisplenitis may develop and result in fixing the displaced organ by adhesions in its abnormal position.

Symptoms.—These vary greatly. There may be no symptoms whatever and the condition may be discovered accidentally in a routine examination; the symptoms are ordinarily surprisingly slight. There may be a dragging sensation or varying degrees of discomfort or pain in the back and side, referred in any direction. The patient often complains of general symptoms, such as headache, insomnia, digestive disturbances, weakness, nervousness, apprehension, etc. Circulatory and other disturbances in different organs may arise from pressure, traction or adhesion of the displaced spleen; thus, there may be nausea, vomiting,

diarrhœa, constipation, jaundice, ascites, bladder and uterine disturbance, etc., depending on the organ interfered with. Intestinal obstruction and strangulation are possible. Twisting of the pedicle may lead to sudden and alarming symptoms due to strangulation, acute enlargement of the spleen, rapidly developing anemia, severe pain, fever, persistent vomiting, or hemorrhage with shock and collapse. In case the torsion is more gradually produced or partial, without strangulation, the symptoms are less violent. Acute perisplenitis gives rise to local pain and sometimes to palpable or auscultatory friction.

Diagnosis.—This in most cases is easy. A mass, resembling the spleen in shape, with a sharp indented edge and pulsating artery at the hilus, capable of replacement into the normal position of the spleen, cannot be mistaken. The absence of dulness in the normal location can sometimes be made out. The position of the displaced organ is apt to be superficial. More difficulty will be experienced if the organ is adherent in its new position or deformed. It has been mistaken for floating kidney, ovarian and uterine tumor, extra-uterine pregnancy, fecal accumulation, etc.

Treatment.—This is guided by the morbid process in the spleen, whether primary or secondary, and by the severity of the symptoms. If discovered accidentally and without symptoms the spleen is better left alone. Caution must be enjoined, also, against informing nervous women of its discovery, as symptoms may date from their knowledge of the condition and progressive neurasthenia may be the penalty. In the majority of cases neurasthenic symptoms are complained of and require general psychic, hygienic, and nutritive treatment. In addition to the general treatment, a well-fitted general abdominal bandage or one made with a special pad for supporting the spleen may give relief if the symptoms are moderate. Enlargement from malaria, syphilis, leukemia, etc., should receive appropriate treatment.

If the symptoms are severe, the health undermined, the spleen enlarged and diseased, operative measures alone offer relief. Both splenopexy and splenectomy are practiced but the present tendency is to favor splenectomy as more certain in results. Marked disease of the spleen is an absolute contra-indication to splenopexy. Leukemia and amyloid disease are contra-indications to any operation. Firm fixation by adhesions to important structures may be a contra-indication. Acute strangulation demands immediate operation. In general the results reported from surgical measures are increasingly good, with a mortality in properly selected cases of less than 10 per cent.

CONGESTION AND INFLAMMATION OF THE SPLEEN.

Synonyms.—Acute and chronic splenic tumor.

Definition.—Active or passive hyperemia, with or without inflammation, acute or chronic in its course, according to the cause and duration. No hard-and-fast line of division can be drawn between congestion and indurative inflammation of the spleen, as both arise from the same causes and occur together as elements or stages of the same processes. This applies more particularly in a clinical sense, but even pathologically

the two elements are so closely related and interdependent that the distinction of one from the other is difficult or impossible in many cases. Hence it seems advisable clinically to consider them together instead of separately. Of all morbid processes involving the spleen, congestive or inflammatory swelling is by far the most frequent clinically.

Etiology.—The causes are those of congestion and inflammation in other organs, namely, irritation or local or general stasis. But such causes act in a special degree upon the spleen above all other organs of the body. The reason for this is not clear in the present state of our knowledge. The sluggish circulation of the organ and its conjectural functional relation in certain processes may be supposed to render the spleen especially liable to congestion and irritation. Irritants may produce both active and passive hyperemia; stasis produces passive congestion.

The most frequent cause of irritative congestion and inflammation is the action of microörganisms and their toxins in the various infectious diseases, *e. g.*, typhoid fever, malaria, syphilis, etc. Less common causes of irritation are the toxic action of drugs, *e. g.*, acetanilid and other coal-tar derivatives, etc., trauma, and local morbid processes in the spleen, *e. g.*, hemorrhage, embolism, etc. Chronic splenic tumor may also arise in various anemic conditions, *e. g.*, pernicious anemia, chlorosis, infantile anemias, etc., and in various diseases of unknown etiology, *e. g.*, splenic anemia, chronic cyanotic polycythemia, rickets, etc. The causes of the indurative inflammation of the spleen in such states, while unknown, may be assumed to be some kind of irritation produced by excessive blood destruction or by chronic toxemia. *Stasis,* as a cause of splenic tumor, acts mechanically by damming back the outflow of venous blood, and arises from diseases of the heart and lungs, leading to obstruction of the general circulation, or from diseases of the portal area causing obstruction to the portal circulation. The causes may act acutely, as in typhoid fever, or chronically as in cirrhosis of the liver, etc., leading respectively to acute or chronic splenic tumor. An acute cause may rarely set up an inflammatory process that continues and becomes chronic.

Pathology.—The most evident alteration is in the size of the organ, which is enlarged, varying with the cause and the duration of the process. Moderate enlargement is the rule in acute diseases, more marked enlargement in chronic diseases. The enlargement may become excessive, especially in chronic malaria and splenic anemia. The organ is usually soft and flabby in acute processes, firm and hard in chronic diseases. Besides congestion with hemorrhages, the organ in acute processes shows slight hyperplasia involving especially the Malpighian bodies, which are in consequence prominent, and in some instances areas of hyaline degeneration and focal necroses. Infarcts occasionally develop from thrombosis of the smaller vessels. Perisplenitis is common. Acute suppurative splenitis or abscess is rare. In the more chronic conditions the tendency is to general induration, involving especially the trabeculæ and their vessels. The whole spleen may be converted into a mass of fibrous tissue with little true parenchyma left. The capsule usually shares in the general fibrosis and may be greatly thickened or involved in circumscribed areas of capsulitis with adhesions. Considerable

pigmentation is commonly seen in anemic states with marked blood destruction and may lead to cyanotic induration. Rupture of the spleen occurs rarely in malaria, typhoid fever, and other conditions.

Symptoms and Diagnosis.—The only important clinical symptoms are splenic tumor and pain, upon which the diagnosis must be based. Other secondary symptoms may depend upon the primary disease, upon complications arising from the enlarged organs, *e. g.*, dislocation, torsion of the pedicle, perisplenitis, infarct, thrombosis, abscess, rupture, etc., or upon pressure effects on surrounding organs, *e. g.*, digestive, cardiac, and respiratory disturbances, gastric hemorrhage, ascites, etc. Pain over the spleen or referred is not constant. It is caused especially by perisplenitis and rapid enlargement with stretching of the capsule. A feeling of weight or uneasiness in the region of the spleen is common and distinct tenderness is elicited by pressure. Splenic tumor is the only constant sign. It may be difficult to detect if the enlargement is not marked, and the consistency of the organ is soft as in acute splenic tumor. Palpation is far more reliable than percussion. In chronic cases the tumor is firm and resistant.

As splenic enlargement is found in such a variety of conditions, many of them of obscure etiology and complicated symptomatology, the recognition of splenic tumor may be of decided diagnostic significance and should never be overlooked or neglected as part of every thorough physical examination.

Pulsating tumor of the spleen has been reported as a curious and rare phenomenon in a few cases of acute splenic tumor (Tulpius, Gerhardt, Prior, Drasche). The pulsation could be distinctly felt on palpation and in some instances seen by inspection. The cases presented a combination believed to be essential to the production of the pulsation, namely, acute splenic tumor, secondary to typhoid fever, malaria, etc., *plus* cardiac disease accompanied by high systolic blood pressure, almost invariably aortic insufficiency.

Treatment.—This is practically that of the primary disease to which the splenic enlargement is secondary. It would be manifestly ridiculous to attempt to treat the "ague-cake" of malaria without curing the malaria with quinine or the splenic hypertrophy of syphilis without mercury and iodide. It would be dangerous to try to reduce the acute splenic tumor of typhoid fever by active depletion of the portal system without regard to the typhoid fever. The cause of the splenic tumor must first be determined and appropriate treatment directed thereto. There are, however, certain special indications for the enlargement itself and for its effects.

Free catharsis may in suitable cases tend to reduce the congested spleen and relieve symptoms of acute stretching of the capsule. The pain, if severe, can be relieved by various local measures, including the application of heat or cold, blisters, dry cupping, strapping the side with adhesive plaster to reduce the respiratory movement of the spleen, or by the administration of morphine, if simpler remedies fail. The application of the *x*-rays over the spleen in cases of marked hypertrophy has been followed in many instances by reduction in its size. In chronic splenic

tumor, even if not of malarial origin, quinine, used in large doses and continued for a long period, has been claimed to be of value. The iodides may have some slight effect in the non-syphilitic cases. Iron and arsenic are indicated for the chronic anemia frequently accompanying splenic enlargement and may incidentally have a favorable effect upon the spleen. In cases of doubtful etiology a course of mercury and iodide should be tried in order to exclude syphilis as a cause.

Splenectomy may be indicated in conditions of great splenic enlargement of long standing when all other treatment has failed, in case of severe and repeated gastric hemorrhages, a state of chronic invalidism, various functional disturbances, or special complications. The enlarged spleen of leukemia and of amyloid disease must be excluded, as experience has shown that the operation is almost always fatal in these conditions.

PERISPLENITIS.

Synonyms.—Capsulitis; capsular splenitis; perisplenic peritonitis.

Perisplenitis occurs as an acute, subacute, or chronic process involving the capsule and peritoneal covering of the spleen locally or generally, according to the origin and extent of the inflammation.

Etiology.—The process originates from local disease (infarct, hemorrhage, abscess, gumma, cysts, tumors, etc.) or general involvement (acute or chronic splenitis of the infectious diseases, splenic enlargement from any cause) of the parenchyma of the spleen or by extension from disease outside of the spleen (pleurisy, pneumonia, peritonitis, tumors, etc.). In old age the capsule may be sclerosed and thickened as part of the process of senile degeneration. Trauma is a rare cause.

Pathology.—The perisplenitis is usually circumscribed, depending upon a focal origin within the parenchyma of the spleen reaching the surface. The lesion may be single or more commonly multiple, several separate points of involvement occurring in the course of the splenic disease to which it is secondary. Where the cause is general or acts extensively, the entire capsule is involved. The peritoneal surface of the organ loses its lustre and is covered with a fibrinous or purulent exudate, according to the severity of the process. Adhesions to surrounding structures usually develop from the areas of inflammation and in rare cases may include pockets of pus. Great thickening of the capsule may result at the point of adhesions and cause marked irregularity of the surface of the spleen. Irregularities may also result from contraction of the fibrous areas. The thickening in certain cases may be marked and show a gristly toughness or become calcified in old age. At autopsy the spleen frequently shows circumscribed areas of thickening on its surface.

Symptoms.—The most important symptom is pain limited to the region of the spleen or more rarely referred in different directions. It may be severe, but generally it is less pronounced and may cause only a sense of discomfort. It is intensified by breathing, movements of the body, lying on the left side, or by pressure. It is remarkable, however, how frequently pain is entirely absent in attacks of perisplenitis, as revealed by autopsy. Fever is an inconstant and variable symptom,

depending on the degree of the inflammatory process and the morbid condition to which it is secondary.

Diagnosis.—The diagnosis must be based on the presence of pain, tenderness, and friction over the spleen. Careful differentiation from diaphragmatic or basal pleurisy must be made, based upon the more definite relation of the pain in pleurisy to the respiration and the associated etiological conditions.

Treatment.—The pain is relieved by local applications, strapping or drugs. The bowels should be kept active. In case of perisplenic collections of pus, surgical interference becomes necessary.

ABSCESS OF THE SPLEEN.

Synonym.—Acute suppurative splenitis.

Etiology.—Abscess of the spleen may occur rarely as an apparently primary condition without discoverable cause. As predisposing causes, exposure to cold, exhaustion, trauma, etc., have been mentioned, acting, it is supposed, by lowering the vitality and resistance of the tissue to the growth of organisms circulating in the blood. Infection of the spleen with abscess formation may arise by extension from inflammatory processes in adjacent organs, as from thoracic empyema, perforating gastric ulcer, general or local peritonitis, etc. Putting aside such exceptional causes, the common causes are septic embolic infarcts and metastatic infection from the circulation in the course of pyogenic infections. Septic embolism arises most frequently from ulcerative endocarditis, in rare cases from abscess of the lung. Metastatic infection of the spleen may be secondary to any inflammatory process from which pyogenic organisms find entrance into the general circulation. Paget found 39 instances of abscess of the spleen in 430 cases of general pyemia. Hydatid cyst of the spleen may become secondarily infected and reduced to an abscess cavity. The specific infectious diseases, especially malarial fever, typhoid fever, and relapsing fever, may rarely cause abscess of the spleen, probably in most instances by secondary infection. There is reason for believing that the specific organism of typhoid fever may lead to suppuration of the spleen in rare instances.

Pathology.—Abscess of the spleen varies from a microscopic collection of pus to one the size of a hen's egg, but in rare instances the entire spleen may be converted into an abscess cavity. In extreme cases the abscess may protrude into and occupy a large part of the abdominal cavity, simulating cyst, ascites, etc. In the non-embolic form the abscess is usually single, large, and likely to be deeply situated. Embolic or metastatic abscesses are usually small and multiple, sometimes coalescing to form large necrotic areas. They are more likely to be located near the surface. If the abscess involves the capsule, circumscribed perisplenitis develops, usually with the formation of adhesions to opposing structures which tend to wall off and limit the inflammatory mass and protect against rupture. The localized peritonitis over the spleen may extend and involve the general peritoneum. Rupture may take place into any adjacent structure, as the general abdominal cavity, stomach,

intestine, pleural cavity, kidney, or externally through the abdominal wall, in rare instances leading to recovery. As a rare result, small abscesses have been found encapsulated with their contents inspissated.

Symptoms and Diagnosis.—Abscess of the spleen is a rare condition clinically, being usually discovered at autopsy. In many cases there are no special symptoms to indicate that the spleen is involved. In general the symptoms are those of suppuration elsewhere, with the addition of pain and tenderness over the spleen and swelling of the organ. When caused by septic embolism the onset is sudden, with all the features of embolism, followed later by the symptoms of suppuration, namely, pain, chills, sweats, irregular pyrexia, leukocytosis with iodophilia, rapidly developing anemia, emaciation, weakness, digestive disturbances, etc. Such symptoms arising from suppuration in the spleen may be masked by similar symptoms caused by the disease to which the splenic abscess is secondary, *e. g.*, ulcerative endocarditis, pyemia, etc. In the non-embolic form the onset may be more gradual, but otherwise there may be no difference so far as the spleen is concerned. The spleen is always swollen, its size depending upon the extent of the inflammatory process. In rare cases of large solitary abscess or where the whole spleen is converted into a pus sac, fluctuation can be elicited. If the abscess exerts pressure against the diaphragm, cough and dyspnœa may result. Perisplenitis is indicated by a friction rub over the spleen. Perforation and rupture into other organs are characterized by special symptoms, such as sudden pain and the coughing up of offensive blood-stained pus with rupture into a bronchus, vomiting or passing of pus and blood per rectum with perforation into the stomach or intestine, etc., followed at once by a marked diminution in the size of the spleen. Exploratory puncture has been done for diagnosis, but its indiscriminate use in diseases of the spleen has led to many fatalities and it should be employed only in carefully selected cases. Examination by the *x*-rays may be of value.

Prognosis.—This is serious both as regards the abscess itself and the primary condition from which it arose. The embolic abscess is only part of a general pyemia, which is almost always fatal. Ulcerative endocarditis, the most frequent cause of embolic abscess of the spleen, is also only a variety of pyemia and is almost necessarily fatal. The non-embolic type may be treated surgically with some hope of success. Spontaneous rupture and evacuation of the abscess through the stomach, intestine, or externally, as described above, may in rare instances be followed by complete recovery. Rupture or extension of the inflammatory process into the general peritoneal cavity, kidney, pleural cavity, etc., leads to a rapidly fatal issue.

Treatment.—This is surgical—aspiration of the contents by puncture, incision with drainage, or extirpation of the entire spleen. The operative mortality is very high, probably from 80 to 90 per cent. The best prospect of success is in the single abscess occurring in the non-embolic cases, as a complication of typhoid or malarial fever, by extension from a local source of infection such as perforating gastric ulcer, the traumatic and idiopathic abscess, etc. The embolic type should not be interfered with, as a rule, being only a complication of conditions in themselves fatal.

INFARCT OF THE SPLEEN.

Etiology.—Next to the kidney, the spleen is the most frequent site of infarction, due to the fact that the arterial radicles of the spleen and kidney are partly of a type known as "terminal arteries" or "end arteries," *i. e.*, without anastomoses. The most frequent cause of splenic infarcation is the conveyance of an embolus from the valves of the left side of the heart in endocarditis to one of the subdivisions of the splenic artery, thus producing occlusion with resulting infarction of the area supplied by the plugged artery. Embolism arising from cardiac thrombi, atheroma or aneurism of the aorta, and pyemia is also a frequent cause. Thrombosis of the radicles of the splenic artery or vein developing in the specific fevers, such as typhoid fever or in marantic and anemic states, is not very rare. In exceptional instances the infarction may originate by backward extension of a thrombus in the splenic vein.

Pathology.—The territory supplied by the plugged artery disintegrates by coagulation necrosis, producing a "white infarct" ("anemic infarct") or, in case of excessive hemorrhage into the area, a "hemorrhagic infarct" of the spleen, consisting of a wedge-shaped area with its base directed toward the surface of the spleen and its apex pointing inward to the site of the embolus. The color of the infarct varies considerably with the nature of the infarct and its age. When fresh it is usually of some shade of yellow or red from the infiltrated blood. Later its color fades and it may become almost white. The "white infarct" is from the first of a pale color, more or less tinged with blood. Subsequently the infarct becomes organized and replaced by fibrous tissue, the contraction of which may ultimately leave only a puckering or scar on the surface of the spleen. The organ may thus be considerably deformed by the cicatrization of multiple infarcts. They may be single or, more commonly, multiple and vary from the size of a pea to that of a large orange, according to the size of the artery which is plugged. If the embolus causing the infarction is infective, the infarct may be converted into an abscess and the spleen may be filled with such abscesses following multiple infarction. When an infarct extends to the surface of the spleen, as it usually does, a circumscribed area of perisplenitis generally results.

Symptoms.—The most reliable symptom is pain developing suddenly in the region of the spleen in the course of valvular disease of the heart, especially malignant endocarditis, or other conditions liable to give rise to embolism. The pain varies in intensity and in some cases may be entirely absent. It is increased by deep respiration or movement. It may last for some days or in exceptional cases for several weeks. Tenderness on pressure and slight swelling of the spleen are the rule. Rigors and fever may occur and, if persistent, indicate infective embolism with probable abscess formation. A peritoneal friction rub is sometimes heard over the spleen, indicating perisplenitis. The symptomatology of infarct of the spleen is often complicated by that of the disease to which it is secondary.

Diagnosis.—This is suggested by the symptoms and signs, above described, occurring in the course of valvular disease of the heart. The

diagnosis is made more certain if signs of infarction of the kidney are also found. Infective embolism with secondary abscess formation in the spleen presents the clinical picture of abscess.

Prognosis.—This is good in simple embolism. In infective embolism it is that of abscess and of the primary disease.

Treatment.—This is directed chiefly toward the relief of pain by means of local applications of heat or cold, dry cupping, strapping the side to limit the respiratory movements, and, if necessary, the use of morphine. Abscess formation requires surgical intervention.

RUPTURE OF THE SPLEEN.

This may be briefly considered because of its interest in connection with enlargement of the spleen in malaria, typhoid fever, etc.

Etiology and Pathology.—The causes are traumatism and preëxisting disease of the spleen. Severe traumatism may lead to the rupture of a perfectly healthy spleen, but far more frequently slight traumatism causes rupture of a spleen already diseased. The morbid conditions that most commonly lead to rupture are excessive enlargement and stretching of the capsule, occurring especially in malaria. In addition, the spleen substance may be soft and friable, the capsule extensively diseased so that its normal elasticity is impaired, and adhesions may further render it more liable to injury from slight strain. Spontaneous rupture may occur in such cases, but generally the rupture is caused by slight trauma induced by strain, coughing, etc. The acute splenic enlargement of typhoid fever, relapsing fever, and the other infectious diseases may likewise lead to rupture. Rupture of the spleen has been observed several times as a complication of pregnancy, occurring especially during labor or eclampsia. Infarct and abscess of the spleen, aneurism of the splenic arteries, and a varicose condition of the veins are less frequent causes.

The rupture may be single or multiple, slight or extensive, involving the capsule alone or extending into the parenchyma. Depending upon the extent of the laceration and the involvement of vessels, the hemorrhage may be slight or so profuse as to cause sudden death. In case of extensive adhesions the hemorrhage may take place into them and remain encapsulated. Rarely it is entirely subcapsular.

Symptoms and Diagnosis.—The occurrence of rupture is indicated by sudden, intense, lancinating pain, with a sensation as though something had torn in the region of the spleen, followed by symptoms of internal hemorrhage with shock—colicky pains, pallor, syncope, faintness; rapid, thready pulse; cold extremities, nausea, vomiting; sighing, rapid respiration; dilated pupils, subnormal temperature, etc. Fever usually follows. The physical examination shows distension of the abdomen, with dulness or fluctuation in the flanks or over the site of the accumulated blood. The size of the spleen, if previously determined, is found reduced. Signs of secondary peritonitis may follow in case the rupture arose from septic infarct or abscess. The *diagnosis* is suggested by the morbid condition of the spleen and by the symptoms and signs. It may be

impossible in case of slight hemorrhage. Differentiation from rupture of hydatid or other cyst or abscess may be difficult, but in these instances the hemorrhage is likely to be slight and in consequence the anemic symptoms of shock are lacking. Differentiation from internal hemorrhage from other organs may be impossible, but this is of minor importance as immediate operation is indicated in all such conditions.

Prognosis.—This is always grave. Spontaneous recovery is possible with slight superficial rupture. Prompt surgical intervention offers a good chance of recovery; without operation death usually occurs within twenty-four hours.

Treatment.—The diagnosis of rupture calls for immediate operation.

THROMBOSIS OF THE SPLENIC VEIN.

Thrombosis with obliteration of the splenic vein and its radicles is of clinical interest chiefly from the point of view of differential diagnosis, the clinical picture being identical with that of splenic anemia.

Etiology.—Thrombosis with obliteration of the splenic vein may result from degeneration or inflammation of the vessel wall in various acute and chronic general conditions, extension of a thrombotic process from the splenic radicles or the portal vein, external pressure by tumors, adhesions, etc., torsion of the vein in movable spleen, trauma, etc. In infancy a special cause is the extension of a pylephlebitis arising from umbilical infection.

Pathology.—The morbid anatomy is that of the vein itself and the changes in the spleen resulting from the venous obstruction. Congestion and enlargement result except in certain instances in which the thrombosis involves exclusively the extrasplenic part of the main trunk with the development of a collateral circulation sufficient to compensate the obstruction; that such a result is exceptional is shown by the fact that splenic congestion and enlargement are the rule in obstruction of the portal vein above the entrance of the splenic vein. The congestion of the spleen leads to the usual fibrotic changes.. If the intrasplenic radicles are thrombosed, hemorrhagic infarction results.

Symptoms.—These are due to the mechanical effects of the venous obstruction, namely, enlargement of the spleen and recurring gastric hemorrhage, and to the secondary effects in disturbance of splenic function and upon neighboring organs. The general symptomatology is identical with that of splenic anemia.

Diagnosis.—It is difficult or impossible to differentiate the splenic enlargement secondary to thrombophlebitis from that of splenic anemia, in view of the fact that the symptomatology is the same and an identical condition of the splenic, portal, and mesenteric veins is common in splenic anemia. Probably many cases diagnosed as splenic anemia are in reality secondary to disease of the portal and splenic veins.

Treatment.—As in splenic anemia, splenectomy is indicated for the relief of severe and recurring gastric hemorrhage or chronic ill health.

AMYLOID SPLEEN.

Etiology.—Broadly considered, the several causes may be included under the heading of a constitutional dyscrasia secondary to chronic cachexias, as only in the rarest instances has the disease been found occurring as an apparently idiopathic process. More specifically, the common causes are chronic suppuration, tuberculosis, and syphilis. Other chronic cachectic conditions, as from nephritis, carcinoma, paludism, leukemia, gout, plumbism, alcoholism, etc., only exceptionally lead to amyloid disease. Of the common causes, chronic suppuration in its various forms stands preëminent. Even in cases due to tuberculosis or syphilis, secondary infections with ulcerative processes are usually found, although not necessarily. Pulmonary tuberculosis with chronic cavity formation (suppuration) is today perhaps the most frequent single cause of amyloid disease. Formerly, infected wounds, suppuration of bones and joints, and chronic surgical infections in general occupied the first place. The length of time necessary to the production of amyloid degeneration in the organs has been determined by careful clinical observations as varying from two and a half to six months after the primary cause has begun to operate.

Pathology.—Amyloid disease of the spleen occurs chiefly in two forms in which the process involves principally the Malpighian corpuscles, constituting the so-called sago spleen, or the parenchyma of the organ, producing diffuse, parenchymatous, amyloid degeneration. In addition, combinations or variations of these principal forms may occur, leading to a variable picture. The sago spleen shows on section small, pinhead-sized, waxy bodies resembling boiled sago grains in place of the Malpighian corpuscles. The organ is of normal size or slightly enlarged and of somewhat increased consistency. This is the common form of the disease observed in the autopsy room. Parenchymatous amyloid degeneration shows on section a translucent waxy appearance involving more or less completely the parenchyma of the entire organ. The spleen in the early stages may be soft and flabby, but later becomes firm and enlarged, with rounded edges and tensely stretched capsule.

The spleen is more frequently involved in amyloid disease than any other organ. In Hoffman's statistics of 80 cases of amyloid degeneration, the spleen was involved in 92.5 per cent., the kidneys in 84 per cent., the intestines in 65 per cent., the liver in 62.5 per cent.; in Litten's 100 cases the corresponding figures were: spleen, 98; kidneys, 97; intestines, 65; and liver, 63 per cent.

Symptoms.—There are no distinctive symptoms, the only splenic features being the enlargement and its mechanical effects, neither of which is constant. Otherwise the patient's general symptoms are due to the primary disease. Only the large lardaceous spleen resulting from widespread amyloid degeneration of the organ attracts special clinical attention. It may reach enormous dimensions, filling the entire left side and in rare instances extending into the right half of the abdominal cavity. The presenting edge is rounded and the organ feels smooth and hard. Tenderness is not elicited by pressure as a rule. A sense of weight

and fulness may be complained of, but actual pain is rare except as a result of rapid enlargement with stretching of the capsule, or from perisplenitis. Disturbances of function in other organs may be caused by the pressure of the enlarged spleen. Anemia of considerable grade may be present, but is attributable chiefly to the primary disease or to the functional disturbances of the various organs. The sago spleen is chiefly of pathological interest, as it never reaches a large size.

Diagnosis.—This is suggested when a hard, smooth, splenic tumor is found developing in the course of a chronic disease (suppuration, tuberculosis, syphilis) that is liable to lead to amyloid degeneration, provided the enlargement cannot be better accounted for by some other cause. Symptoms of amyloid disease of the kidneys, intestines, or liver would confirm the suspicion and make the diagnosis probable, if not certain. The most important symptoms of amyloid degeneration of these organs are as follows: of the liver, a smooth, firm, painless, marked enlargement; of the intestines, persistent, uncontrollable diarrhœa; of the kidneys, dropsy, a large amount of pale, clear urine of low specific gravity containing usually considerable albumin and globulin with casts. Marked anemia and pallor occur in most cases, and are due to the primary disease as well as its effects and complications.

Treatment.—This is chiefly that of the primary disease; syphilis can be cured and chronic suppuration is often amenable to successful surgical treatment. The same is true of certain forms of tuberculosis, *e. g.*, involving the bones, joints, glands, etc. If the cause can be removed, the secondary amyloid disease will stop its further destructive changes. The destruction already accomplished cannot be repaired, but if it has not reached a severe grade its existence may be compatible with a long life. General tonic treatment is indicated for the anemia and malnutrition. Iron and arsenic may be tried and the syrup of the iodide of iron has been found especially valuable. Fresh air, an abundant nourishing diet, and a change of residence are of great assistance.

TUMORS OF THE SPLEEN.

New-growths of all kinds, whether benign or malignant, primary or secondary, are of rare occurrence in the spleen compared with their general frequency in other organs. The following varieties have been observed:

Benign Tumors.—Fibroma.—A rare condition, occurring as single, sometimes multiple, small, round nodules, about the size of a walnut.

Lymphangioma.—Two cases have been reported by Fink. Both were multiple and extensively invaded the spleen substance, with protrusions on its surface.

Angioma Cavernosum.—The tumors are sometimes of enormous size and they may lead to chronic ascites, characterized by large quantities of a blood-stained fluid. They are believed sometimes to degenerate into serous cysts. Langhans' case was one of pulsating angioma observed during life.

Malignant Tumors.—**Carcinoma.**—Primary epithelial growths of the spleen are so rare that their occurrence has been doubted, especially as no epithelial tissue occurs in it normally, although it is theoretically not impossible to conceive of the congenital inclusion of embryonic epithelium. Some of the cases reported as primary are undoubtedly secondary, the primary focus having been overlooked. Other cases are instances of sarcoma or of chronic endothelial hyperplasia. Litten found but ten cases reported as primary carcinoma and in a majority of these the diagnosis was open to criticism. While, therefore, the possibility of primary carcinoma of the spleen cannot be denied, its proof has not been satisfactorily established. *Secondary metastatic carcinoma* of the spleen is also of very infrequent occurrence.

Sarcoma.—While rare, sarcoma is the most important of all forms of primary tumor of the spleen. Jepson and Albert[1] have collected 32 cases from the literature, but the diagnosis of many of these is questionable, probably including instances of lymphadenoma (Hodgkin's disease) and endothelial hyperplasia (Gaucher's disease). The varieties of sarcoma include round-cell sarcoma, lymphosarcoma, endothelial sarcoma, and fibrosarcoma. The growth is usually multiple, consisting of nodules varying in size from a cherry to a hen's egg. The spleen is usually greatly enlarged and its surface may be irregular from the projection of the masses.

The symptoms and signs are: rapid enlargement of the spleen, sometimes with palpable nodules; pain over the spleen, radiating over the abdomen or upward; tenderness on pressure; and the cachexia and general symptoms accompanying malignant growths elsewhere. The clinical diagnosis can never be made with any degree of certainty.

Secondary sarcoma is relatively less infrequent, but it is remarkable how seldom the spleen is invaded even by metastatic growths.

CYSTS OF THE SPLEEN.

Cysts of the spleen belong to three classes, as follows:

I. **Simple Cysts,** *i. e.*, serous, hemorrhagic, and lymph cysts.

II. **Dermoid Cysts.**

III. **Parasitic Cysts,** *i. e.*, hydatid cyst, Cysticercus cellulosæ, and Pentastomum denticulatum.

I. **Simple Cysts.**—These, which are comparatively rare, are classified as *serous*, *hemorrhagic* (*blood*), or *lymph cysts*, according to their contents, as in other respects they have no essential differences. The fluid of *serous cysts* is clear, of low specific gravity (1003 to 1010), and non-albuminous. *Hemorrhagic cysts* are characterized by containing considerable blood or blood remnants, the contents varying in color and consistency with the amount of blood, age, alterations, etc. *Lymph cysts* contain a fluid with the characteristics of lymph, *i. e.*, albuminous, of high specific gravity, and with a tendency to spontaneous coagulation when exposed to the air. All three types of cyst always contain cholesterin

[1] *Ann. Surg.*, 1904, xl, 80.

crystals in varying amount and may undergo degeneration into so-called *cholesterin cysts,* characterized by a fatty detritus loaded with cholesterin crystals.

Etiology.—Some of the cysts arising in the capsule may be caused by the degeneration of inclusions of peritoneal endothelium (Renggli). Others are caused by degeneration of the Malpighian bodies or spleen pulp or from degenerated lymphangiomas. True retention cysts do not occur, due to the absence of tubular glandular structure, although certain blood and lymph cysts may perhaps arise by occlusion of blood or lymph vessels with ectasis and retention. Trauma and traction exerted by adhesions or disease of vessel walls may lead to hemorrhage, causing hematoma which may become encapsulated and converted into a cyst. A serous or lymph cyst may be converted into a blood cyst by hemorrhage. Repeated hemorrhage into a cyst may cause successive enlargements of the cyst. By these various processes simple cysts of the several types may arise, varying in character according to the cause and the structure in which they originate. In general, trauma is the most frequent single cause of cyst formation in the spleen. From trauma blood cysts may develop quite rapidly, reaching their maximum size within a few weeks; in other cases the full size may only be attained after years.

Pathology.—Simple cysts may be single or multiple, unilocular or multilocular, very small or large, sometimes reaching the size of a man's head. They are usually lined by endothelium, although in old cysts this may not be found. They may be situated in any part of the spleen, commonly in the lower anterior part, and especially in or beneath the capsule. Old cysts may have thick, calcified walls. Perisplenic adhesions may form over the site of the cysts. The spleen may be dragged down by the weight of enormous cysts into any part of the abdominal cavity. Rupture of the cyst or infection of its contents is very rare.

Symptoms.—Small cysts are of no clinical importance, only large cysts leading to symptoms and complications call for medical attention. The symptoms are usually produced mechanically by the traction or pressure of the large cyst. Thus, a feeling of weight or fulness, tenderness, and digestive, urinary, respiratory, or other functional disturbances are common. Actual pain is unusual, except in case of perisplenitis, dislocation of the spleen by traction, rapid stretching of the capsule by large hemorrhages, or other accidental complications. In addition to such common symptoms, the cyst may produce enlargement of the abdomen over its site, and upon palpation fluctuation is usually obtained. Suppuration of the cyst, which is rare, produces the symptoms of abscess.

Diagnosis.—This must be based upon the discovery of a fluctuating enlargement definitely arising from the spleen, by diagnostic puncture or by exploratory operation. Fluctuation cannot always be elicited and even puncture may prove negative if the contents are thick. In such cases cyst can only be suspected by the outline of the tumor, and exploratory laparotomy may be required to determine its nature. If a cystic spleen is dislocated into the abdomen, diagnosis may be very difficult.

In the differential diagnosis, cyst of the left kidney, hydronephrosis,

ovarian cyst, and hydatid cyst of the left kidney or left lobe of the liver must be carefully considered. All of these conditions, especially ovarian cyst, have been diagnosed in cases of cyst of the spleen. Other possible sources of confusion are loculated pleural effusion of the left base, cyst of the pancreas, and solid tumors or inflammatory masses in the upper left quadrant of the abdomen. Simple cyst can be differentiated from hydatid cyst only negatively, *i. e.*, by obtaining by puncture fluid free from hydatid elements, which, of course, does not exclude the possibility of the cyst being hydatid. On the other hand, hydatid cyst is proved by finding in the fluid hooklets, scolices, bits of lamellated membrane, etc., or by other evidences of echinococcus disease. Hydatid cyst of the spleen is made probable if cystic disease of the liver can at the same time be determined. Hydatid fremitus is an inconstant and unreliable sign that can be simulated in other conditions. Diagnostic puncture, if practiced, should be made at the bottom of a dependent part of the cyst, in order to increase the chance of obtaining hydatid elements which settle by gravity to the lowest part of the cyst. Puncture should be performed only with a full understanding of its danger.

Treatment.—A close-fitting abdominal bandage may be worn to support the weight of the cyst, relieve symptoms, and prevent dislocation of the spleen. Surgical intervention is required when the cyst is very large, when it causes marked functional disturbances and troublesome symptoms, when it becomes infected, when the spleen is dislocated into the abdominal cavity, and in the presence of other serious complications. Splenectomy and partial resection of the spleen are the operations of choice advocated by modern authorities. Powers[1] records the operative results in 28 cases from the literature. Of these, 10 were treated by splenectomy and all recovered; 5 were treated by resection of the cyst, 4 recovered and 1 made a relative recovery; 5 were treated by incision and drainage, 3 recovered, 1 made a relative recovery, 1 died of sepsis; the remaining 8 cases were treated by puncture, incision and injection, and marsupialization.

II. **Dermoid Cysts.**—Andral recorded the only instance known.

III. **Parasitic Cysts.** (*a*) **Hydatid Cysts.**—Hydatid or echinococcus cysts of the spleen occur in about 3 or $3\frac{1}{2}$ per cent. of all cases of hydatid disease (Litten). Hirschberg, in 1888, found in the literature 41 cases of primary echinococcus cyst of the spleen and 37 cases in which the spleen and other organs were involved. In the statistics of the disease in North America collected by the writer,[2] in 1901, among 241 cases, 9 instances of involvement of the spleen were found (3.7 per cent.).

Hydatid cyst of the spleen is always unilocular and usually single, but exceptionally more than one cyst may be found. The cysts may occupy any portion of the organ and may reach a large size. Occasionally hydatid cysts develop not in the spleen proper, but in the gastrosplenic omentum, involving the spleen secondarily by extension.

Hydatid disease of the spleen follows the same course characteristic of it elsewhere. The symptoms are similar to those of simple cyst. Inflammation of the cyst is liable to occur, in case of which the symptoms

[1] *Ann. Surg.*, 1906, xliii, 48. [2] *Am. Jour. Med. Sci.*, 1902, cxxiii, 124.

are those of abscess. The differential diagnosis from simple cyst has been considered above. Diagnostic puncture and exploratory laparotomy are the chief means. Diagnostic puncture is not devoid of danger. It may be followed by serious symptoms of toxemia, sometimes resulting in death, may lead to fatal general peritonitis if the cyst is infected, and may permit the escape of living hydatid elements capable of disseminating the disease in the peritoneal cavity. While such sequelæ are fortunately not common, they should be considered possible and exploratory puncture should be restricted to exceptional cases. If an exploratory operation is warranted, preliminary puncture through the abdominal wall should never be practised. The diagnosis of hydatid cyst must be made from the same conditions as in simple cyst of the spleen.

The *prognosis* is always grave when the cyst is large or reaches the surface of the spleen, because of its tendency to rupture. Destruction of small hydatid cysts may occur with calcification.

The *treatment* is strictly surgical, either by extirpation or incision. Total splenectomy is the operation of choice, unless contra-indicated.

(*b*) **Cysticercus Cellulosæ and** (*c*) **Pentastomum Denticulatum.**—Each of these parasitic cysts has been found in the spleen in rare instances. They consist of small cystic bodies that may become obliterated and calcified. They never produce clinical symptoms and are of pathological interest only.

SPLENIC ANEMIA.

Definition.—A disease, possibly an intoxication of unknown nature, characterized by great chronicity, primary progressive enlargement of the spleen which cannot be correlated with any known cause (primary splenomegaly), anemia of a secondary type with leukopenia, a marked tendency to hemorrhage, particularly from the stomach, and in many cases a terminal stage with cirrhosis of the liver, ascites, and jaundice (Banti's disease). This definition, adopted from Osler, covers the main features of a disease picture that has only in recent years come into prominence. Previously great confusion existed in the classification, and it cannot be claimed that our present understanding permits of any exactness. The present attempt at classification must be regarded rather as tentative, pending further investigation and the solution of the question of specific cause. Many observers believe that the group of cases now included under the name of splenic anemia, as defined above, will ultimately be resolved into subdivisions of different etiology. The name "splenic anemia" is therefore used at present as covering a certain group of cases with a fairly definite symptom-complex that cannot be explained by any known cause. It is now generally believed, however, that this symptom-complex, while probably including many cases of different nature, still, after the exclusion of all such cases, embraces a residuum of cases of specific etiology. And to this theoretical residuum of cases, then, the term "splenic anemia" should ultimately be restricted.

The proposition advanced by Osler and now widely accepted, that "the conditions separately described in the literature as primitive spleno-

megaly, splenic anemia, splenomegalic cirrhosis of the liver, or Banti's disease, are stages of one and the same malady," is tentatively assumed by the writer. On this assumption, primary splenomegaly and splenomegaly with cirrhosis of the liver (Banti's disease) are regarded as initial and terminal stages respectively of splenic anemia.

Since writing the article on Splenic Anemia for the first edition of this work, in 1907, several morbid affections, previously included under splenic anemia, have been differentiated and withdrawn from this group. Thus the Gaucher type of splenomegaly appears to constitute a pathological entity. A great group of cases occurring in infants in countries bordering the Mediterranean, previously called infantile splenic anemia, has proved to be a form of kala-azar and due to infection with leishmania. The newly discovered serological tests for syphilis have made it possible to differentiate certain cases of syphilitic splenomegaly otherwise included under splenic anemia.

Incidence.—Since attention has been directed to this affection it has been found to be not rare. It is widely distributed without special geographical or racial incidence. *Sex:* Males predominate in the proportion of 30 males to 18 females. *Age:* The great majority of cases occur between the ages of twenty and forty; below ten and above fifty cases are unusual; cases beginning in infancy or early childhood and surviving to adult life have been reported, but such cases as well as the great group of infantile cases of splenomegaly in general are still too much confused to permit of classification. *Family Incidence:* It is doubtful whether multiple family cases ever occur, although such incidence is notable in the Gaucher type of splenomegaly which has commonly been included as a variety of splenic anemia.

Pathology.—Briefly summarized, the essential pathology consists of hyperplasia and fibrosis of the spleen, anemia of a secondary type, and cirrhosis of the liver as a terminal development in certain cases (Banti's disease).

Spleen.—The enlarged spleen shows a general hyperplastic fibrosis of varying degree involving the capsule, the reticulum of the pulp, and in particular the Malpighian bodies. The pulp and Malpighian bodies are more or less sclerosed and atrophied and often the fibrous Malpighian bodies show hyaline degeneration. The pulp sinuses or blood spaces in many cases show varying grades of hyperplasia of the lining endothelial cells. Areas of hemorrhage, perisplenic adhesions, and infarcts are occasionally found.

Liver.—This shows no characteristic changes except in the infrequent cases presenting the symptom-complex described by Banti and now generally regarded as a terminal stage of splenic anemia. In such cases varying degrees of atrophic interlobular cirrhosis occur with reduction in the size of the organ. The slight enlargement observed in the ordinary cases of splenic anemia is caused by chronic passive congestion.

Veins of the Portal System.—As originally described by Banti, many of the cases show calcification and stenosis of the veins of the portal system, more particularly the portal and splenic veins, although the mesenteric veins may sometimes be involved. Thrombosis of these veins may

also occur and by organization cause complete obliteration of the circulation.

Lymph Glands.—These are not enlarged to any extent and show none of the changes characteristic of Hodgkin's disease. According to Dock and Warthin, there is a new formation of small hemolymph nodes, especially in the mesenteric fat, with deposit of blood-pigment, giving evidence of hemolysis.

Bone-marrow.—This may show the compensatory changes secondary to any severe anemia, *i. e.*, proliferation of the erythroblastic tissue. The changes elsewhere may be regarded as accidental or secondary.

Pathogenesis.—The real cause is unknown. Bacteriological examination of the organs, cultures, and animal inoculation have all proved negative. Syphilis, malaria, and other common infections can be eliminated from consideration.

Much theorizing has been indulged in by writers in discussing the possible rôle played by the spleen, but such theorizing must be mere conjecture in the absence of any real knowledge of the essential functions of the spleen. Banti's view may be cited in point: that the spleen is primarily at fault because (1) the splenomegaly always precedes all other manifestations; (2) splenectomy cures; (3) the pathological anatomy of the spleen is characteristic. However, the last point is far from being conceded by independent observers and the other points cited by Banti are inadequate to sustain his claim. That the splenic enlargement is the earliest sign observed is admitted, but proves nothing as to the exciting cause of this enlargement. The striking benefit, amounting often to a cure, that results from splenectomy might seem at first sight to indicate that the spleen was the primary seat of the morbid process. But there are now known to be a considerable number of affections, most of them admittedly not depending upon *primary* disease of the spleen, that are greatly or even equally benefited by splenectomy, at least in certain instances. This is true of the following affections: (1) splenomegaly secondary to traumatic or infective pylethrombosis; (2) splenomegaly resulting from chronic tuberculosis, syphilis, and other specific infections; (3) Gaucher's type of splenomegaly; (4) splenomegaly associated with Hanot's hypertrophic biliary cirrhosis of the liver and with other types of hepatic cirrhosis; (5) splenomegaly of congenital hemolytic jaundice; (6) pernicious anemia, with or without splenic enlargement; (7) catarrhal jaundice threatening acute yellow atrophy of the liver (Eppinger).

If, in all these diverse conditions, splenectomy results in a striking arrest of symptoms and a general improvement that amounts sometimes to an apparent cure, it is evident that a disturbance of splenic function is at least an important contributory factor to the morbid state, but not necessarily the primary or essential factor. Similarly in splenic anemia the benefit from splenectomy indicates that a disturbance of splenic function contributes at least some factor, but not necessarily the primary factor, in producing other secondary changes. It does not seem reasonable to go further at present in attempting to define the relation of the spleen to the morbid process of splenic anemia. If a conjecture were permitted,

it might be suggested that when enough becomes known it may be found that in diverse chronic infections and intoxications the spleen shares with other organs in a disturbance of function, in some bearing the brunt of the attack and contributing secondarily an important new factor in a morbid chain, the removal of which factor by splenectomy may be sufficient to arrest the further advance of the general disturbance. If such conjecture be substantiated, it may become necessary to eliminate entirely the conception of splenic anemia as a morbid entity and to correlate it merely as a secondary disturbance of splenic function with many other morbid processes that include the spleen among the organs involved in a more or less general chronic infection or intoxication.

Symptoms.—**Splenomegaly.**—The spleen is greatly enlarged. It usually reaches the navel and often the anterior superior spine of the ilium, and it may even pass the median line and occupy a considerable part of the right side of the abdomen. In weight it varies between 26 and 190 ounces, averaging about 62 ounces. The organ feels smooth and firm and preserves its characteristic form, with its sharp edge and notches presenting anteriorly. The enlarged spleen causes very little pain except when perisplenitis or infarct occurs. There may be some tenderness on pressure and a certain amount of discomfort. The splenic enlargement is the first development and may last for years before anemia appears.

Anemia.—This follows but never precedes the splenic enlargement, a sequence that has been observed in many cases. For years with marked enlargement of the spleen there may be no anemia or only a slight reduction of the hemoglobin. Sooner or later anemia develops and persists, intensified in certain cases periodically by loss of blood from hematemesis, from which the tendency to restoration is impaired and delayed.

The anemia is of the secondary type and the blood picture presents nothing distinctive. In Osler's series the red corpuscles averaged 3,425,000, with extremes of 2,187,000, and 5,200,000 per cmm. (the latter case showing only 75 per cent. of hemoglobin). The loss of hemoglobin is proportionately much greater than that of the red corpuscles and is pronounced, as a rule. In Osler's series the hemoglobin averaged 47 per cent., with extremes of 25 and 75 per cent. Poikilocytosis is rare and nucleated red corpuscles (normoblasts) are seen only occasionally in advanced stages. The *leukocytes* show a marked reduction, as a rule. In the uncomplicated cases of Osler's series the average count was 3850 per cmm. and only one case, admitted to the hospital shortly after a profuse hemorrhage, showed a count as high as 12,500. In rare cases a moderate and persistent leukocytosis has been reported, but such cases are exceptional and the presence of leukocytosis in the absence of complications should raise a doubt as to the diagnosis. The differential leukocyte count shows nothing characteristic. A relative lymphocytosis is sometimes observed.

Hematemesis.—As pointed out by Osler, gastric hemorrhage is a special feature of the disease, occurring in 8 of his 15 cases and in 7 of 19 cases observed by members of the Association of American Physicians. In most cases the hemorrhage is due to mechanical causes related to the enlarged spleen and not necessarily to cirrhosis of the liver. The bleeding

may come from congestion and diapedesis of the gastric mucosa, from gastric erosions, or from rupture of varicose veins of the œsophagus. The bleeding is profuse and may recur at intervals over a long period of years. In a case seen by the writer large quantities of blood had been vomited at intervals of about a year, over a period of eleven years. Other forms of hemorrhage may occur, especially in the advanced stages with anemia, such as epistaxis and oozing from the gums, and more rarely retinal hemorrhages, ecchymoses in the skin, etc.

Pigmentation of the Skin.—A diffuse bronzing or, in some cases, a peculiar steel-gray discoloration of the skin has been observed in a considerable minority of the cases, rarely so extreme as to suggest Addison's disease. In a few cases the pigmentation has been patchy and intensified by an accompanying leukoderma.

Ascites.—This may occur in the last stage with cirrhosis of the liver (Banti's disease) and also in some cases in which cirrhosis of the liver has been excluded by operation or autopsy. In the latter cases the ascites is probably caused by the enlarged spleen in association with anemia.

Œdema of the ankles may be an occasional symptom in cases with considerable anemia or with ascites.

Jaundice.—Jaundice, moderate in degree, occurs occasionally either in association with cirrhosis of the liver or independently of such association, related to circulatory disturbances arising from the enlargement of the spleen, or from pressure by the spleen. The *liver* is of normal size in most cases. Frequently, however, it is slightly enlarged so that its edge can be felt an inch or two below the ribs. With terminal cirrhosis the organ may be contracted and reduced in size.

Digestive disturbances, especially loss of appetite, and constipation, less frequently attacks of vomiting, diarrhœa, colic, etc., may occur, although they are not very prominent features in the general run of cases.

The *heart* may show the signs common to all forms of pronounced anemia, *e. g.*, hemic murmurs, palpitation on exertion, dilatation, etc.

The *urine* may show traces of albumin and in rare cases nephritis has been described.

The *temperature* is usually normal but occasional exceptions occur. In the advanced stages there may be a tendency to an afternoon rise of temperature to 100° or higher, and in rare cases it may be irregular or of a hectic type without known complication to account for it. The temperature in such cases has been compared with that frequently observed in other severe anemias.

Course and Prognosis.—A special feature of the disease is its remarkable chronicity, dating from the discovery of splenic enlargement. A duration of ten or more years is usual. The patient enjoys a fair degree of health and may be able to pursue his vocation until the more serious symptoms arise. Periods of improvement or of aggravation of symptoms may occur from time to time but the tendency is to a slow progressive development. Death results from progressive asthenia, cardiac syncope, hemorrhage, or intercurrent infection.

Diagnosis.—After what has preceded in the description of the limitations of our understanding of this complicated group of cases, it will be

appreciated that a diagnosis should never be undertaken without due consideration of the many possible sources of error, and even then it is only tentative, never quite certain. Early diagnosis is manifestly impossible; later, when the splenic enlargement is associated with anemia, the diagnosis is probable only after excluding every other cause. The failures of the most eminent clinicians and the revelations of the autopsy-room should be sufficient warning to the less experienced. The conditions that need careful consideration in the differential diagnosis are:

Leukemia.—This is excluded by the absence of its characteristic blood picture, except in rare cases of so-called aleukemic leukemia with intermissions of the leukemic state of the blood.

Hodgkin's Disease.—It is still open to doubt whether a primary splenic form of this disease without involvement of the lymph glands occurs, as claimed by some.[1] If it does occur, it must be rare and its differentiation from splenic anemia clinically might be impossible. Moderate enlargement of the spleen in Hodgkin's disease is common but the association of enlarged lymphatic glands helps to differentiate it from splenic anemia.

Pernicious Anemia.—While the splenic enlargement sometimes occurring in pernicious anemia is usually slight, it must be recognized that exceptional cases occur in which the spleen may attain a size comparable to that of splenic anemia. The writer has seen three such cases, in each of which the diagnosis of splenic anemia had been made, based upon the great size of the spleen in spite of the presence of a blood picture typical of pernicious anemia. It is doubtful whether splenic anemia ever exhibits the extreme degree of anemia or the other blood changes which together constitute the blood picture of pernicious anemia.

Congenital Hemolytic Jaundice.—This well defined condition ought not to be confused with splenic anemia, if its distinguishing characteristics are kept in mind, as follows: its appearance in early life, usually congenital and often in more than one member of a family, with prolonged chronicity into adult life; great enlargement of the spleen; persistent, moderate jaundice, accompanied by absence of clay-colored stools, absence of bilirubin and presence in excess of urobilin and urobilinogen in the urine; moderate anemia, subject to periodical access and characterized by reduced osmotic resistance of the erythrocytes to hemolysis, with marked anisocytosis, anisochromia and other changes in the staining of the red corpuscles; and a state of fair general health. An acquired form of the disease in adults is also recognized.

Cirrhosis of the Liver.—Several types of hepatic cirrhosis with splenic enlargement may be mistaken for splenic anemia:

1. *Syphilitic Cirrhosis of the Liver.*—Syphilis of the liver, whether congenital or acquired, may be associated with splenic enlargement, not as a rule great, although in rare cases the spleen may fill the whole left side of the abdomen. The liver in such cases is usually irregularly enlarged, an important differential point. Later the liver may be contracted and reduced in size. There may be considerable anemia, jaundice, ascites, hematemesis, etc., all suggesting a late stage of splenic anemia (Banti's

[1] See Wade, *Jour. Med. Research*, 1913, xxix, No. 141, 209.

disease). A persistent leukocytosis occurs in certain cases, a point seldom seen in splenic anemia in adults. A definite history of syphilis, other evidences of syphilis, a positive Wassermann reaction, or the result of specific medication may clear up the diagnosis.

2. *Atrophic Cirrhosis of the Liver.*—This often presents enlargement of the spleen, slight or moderate as a rule, but exceptionally enormous. Differentiation from splenic anemia must be based on the history of alcoholism, the absence of much anemia except in the terminal stage or after profuse hemorrhage, the reduced size of the liver, the collateral superficial circulation, the history of the late development of the splenic enlargement subsequent to the hepatic symptoms, and a general consideration of the case in its history and all its features. Banti's late stage of splenic anemia with cirrhosis of the liver, ascites, jaundice, etc., may be impossible of differentiation from primary cirrhosis of the liver with secondary splenic enlargement except by the absence of a history of alcoholism and the knowledge that the splenic enlargement had existed for a long time prior to the development of signs of cirrhosis of the liver.

3. *Hypertrophic Cirrhosis of the Liver (Hanot's Cirrhosis).*—This disease, occurring mostly in young people, is characterized by a very chronic and marked enlargement of the liver, considerable enlargement of the spleen, chronic icterus of varying degree, a hemorrhagic tendency, and sometimes by leukocytosis, fever, etc. The great size of the liver, firm and smooth, the long duration of this enlargement, the chronic jaundice, and the general prominence of the hepatic and biliary symptoms serve to differentiate the affection from splenic anemia.

4. *Hemochromatosis.*—This is characterized by chronicity, the deposit of an iron-containing pigment in the skin and organs leading to the production of sclerosis of the liver, spleen, and pancreas, with enlargement of the liver and to a less extent of the spleen, bronzing of the skin, and, as a terminal event, diabetes. The hepatic and splenic enlargement develop progressively at the same time. A slight anemia may also occur.

5. *Cirrhosis of the Liver with Splenomegaly in Infancy and Early Childhood.*—This includes a very large and complicated group of cases that are still confused and little understood. Anemia is usually but not invariably associated. Cirrhosis of the liver is also not invariable. Ascites, jaundice, and hemorrhages from the stomach may occur. Many cases are clearly secondary to such conditions as rickets, syphilis, scurvy, marasmus, etc., but others occur without evident cause. Infantile kala-azar can be differentiated by the presence of leishmania. It is possible that some of these cases of splenomegaly in infants may be instances of splenic anemia, but a positive diagnosis of splenic anemia in early life is always hazardous.

Splenomegaly from Portal Obstruction.—The complete picture of splenic anemia may be caused by obstruction of the portal or splenic vein, the obstruction arising within or outside of the vessel. The differentiation from splenic anemia during life is usually out of the question, and even after autopsy it may be impossible to determine the sequence, *i. e.*, whether the portal obstruction caused the splenomegaly or the disease of the spleen led to thrombosis or sclerosis of the vein.

Gaucher's Splenomegaly.—This is discussed on page 962.

Chronic Splenitis in the Infectious Diseases.—The enlarged spleen secondary to diseases, such as malaria, syphilis, tuberculosis, uncinariasis, kala-azar, malignant endocarditis, etc., requires careful differentiation from splenic anemia. These diseases must always be excluded by appropriate examinations and tests before entertaining the diagnosis of splenic anemia. In particular the serological test for syphilis should never be omitted, as its application in the past few years has demonstrated the syphilitic nature of many cases that had been classed under splenic anemia. The possibility of kala-azar should also be kept in mind, especially in infantile cases in countries where leishmaniasis is endemic.

Amyloid Spleen.—This is always secondary to chronic syphilis, tuberculosis, suppurative processes in the body, etc., and the diagnosis is suggested by the presence of one of these conditions, usually with evidences of amyloid disease of other organs.

Neoplasms of the Spleen.—These are rare, but primary malignant disease might be suggested by an irregular and rapid enlargement with the accompanying constitutional symptoms. Secondary malignant disease could be diagnosed only by its relation to other foci of the disease. Benign growths could be differentiated only by operation.

Tumor of the Left Kidney.—The writer witnessed a laparotomy performed by an eminent surgeon for supposed splenic anemia, in which malignant disease of the left kidney caused an enormous abdominal tumor simulating an enlarged spleen. Such an error could rarely occur with careful methods of examination.

Gastric Ulcer.—The recurring hemorrhages of splenic anemia suggest gastric ulcer as a cause. The first case of splenic anemia ever seen by the writer was diagnosed as gastric ulcer by an eminent authority. The enlarged spleen and other features of splenic anemia should serve to differentiate, although it is possible for the two conditions to coexist.

Treatment.—General.—The medical treatment is purely symptomatic; symptoms and complications must be treated on general principles. For the anemia, iron and arsenic may be tried, with rest, fresh air, abundant feeding, etc. Many cases are reported as improved by such simple measures, but the favorable effects are only temporary. The application of *x*-rays over the enlarged spleen has proved to be of some palliative value but no lasting results have been obtained. Recently salvarsan has been tried in a few cases with reported apparent cure, but its use has been too recent and limited to warrant any judgment of its value.

Splenectomy.—Originally proposed by Banti on theoretical grounds, splenectomy has proved to be the only method of real therapeutic value. It may be concluded that it effects a permanent cure in the great majority of patients who survive the operation, if it is undertaken before the terminal stage of the disease. Even after the advent of cirrhosis of the liver and ascites a good chance of operative and therapeutic success remains. Exact statistics of any magnitude are still wanting but the general testimony from all sources supports the above conclusions. As to the operative risk of splenectomy the following statistics are available: The operative mortality from splenectomy *for all causes* in 739 cases,

to 1905, was 26.6 per cent. (Carstens[1]), and in 708 cases, to 1908, was 27.4 per cent. (Johnston[2]). The operative mortality from splenectomy *for splenic anemia* in 32 cases, to 1906, was 28.1 per cent. (Armstrong[3]); in 61 cases, to 1908, was 19.5 per cent. (Johnston[4]); for splenic anemia before the terminal stage of cirrhosis of the liver and ascites in 82 cases, to 1913, 13.4 per cent.; and in the terminal stage in 16 cases, to 1913, 56.2 per cent. (Rodman and Willard[5]). The operative mortality from splenectomy for splenic anemia, including all stages, in 18 cases, from 1905 to 1912, in the Mayo clinic alone, was 11.1 per cent. (Giffin).

The most valuable available statistics on the ultimate results of splenectomy for splenic anemia are those from the Mayo clinic, as follows: Of 16 among 18 patients who survived the operation, 12 have remained in excellent health during a period varying from a few months to seven years; 2 are improved; 1 improved for several months, but died with symptoms of hepatic cirrhosis three years after operation; 1 died two and one half years after operation from unknown cause; 4 of 5 patients who showed evidence of cirrhosis of the liver at operation (1 died from operation) are in excellent health, 1 seven years after operation (Giffin[6]).

It must be admitted that the above statistics are not above criticism in reference to the diagnosis of splenic anemia, cases of Gaucher's type of splenomegaly and other conditions doubtless being included.

The combination of splenectomy and Talma's omentopexy has been practiced in many cases and seems to be the logical procedure, at least in advanced stages of the disease.

GAUCHER'S SPLENOMEGALY.

This rare disease, formerly supposed to be a variety of splenic anemia, is characterized by a unique pathology which seems to differentiate it from all other types of splenomegaly. Only about fourteen cases verified by microscopic examination and perhaps as many more diagnosed on clinical grounds have been reported. It was first described by Gaucher, in 1882, under the designation, "epithélioma primitif de la rate," primary epithelioma of the spleen. Subsequently it has been reported under a variety of names.

Pathology.—The peculiar feature involves the spleen, liver, lymph glands and bone marrow, and consists in the presence of masses of peculiar large cells and iron-containing pigment.

The *spleen* is enormously enlarged, but preserves its form. In one case it weighed almost 15 pounds and in 13 cases, including a child, it averaged 7.2 pounds. There is a varying amount of fibrosis. Microscopically the organ is characterized by the presence of masses of peculiar, large, round or oval cells with relatively small, round, single or multiple nuclei. These cells suggest atypical, swollen endothelial cells. The spleen structure is more or less widely replaced by large, irregular, alveolar

[1] *New York Med Jour.*, 1905, lxxxii, 1051.
[2] *Ann. Surg.*, 1908, xlviii, 50.
[3] *Brit. Med. Jour.*, 1906, ii, 1273.
[4] *Loc. cit.*
[5] *Ann. Surg.*, 1913, lviii, 601.
[6] *Amer. Jour. Med. Sci.*, 1913, cxlv, 781.

spaces, representing the greatly dilated venous sinuses, filled with the peculiar large cells. Similar cells are scattered irregularly throughout the pulp. An iron-containing pigment is found between the connective tissue fibres of the trebeculæ, within the endothelial cells of the capillaries and in many of the typical large cells in advanced cases.

The *liver* is enlarged in proportion to the duration of the disease, its average weight in five adult cases being 7.2 pounds, in one case reaching 10 pounds. There is marked increase of interlobular connective tissue which is invaded by masses of the same type of peculiar cell found in the spleen. Individual cells of the same character are found in the sinusoids of the liver lobules. The parenchyma cells are well preserved. Pigment is found in the capsule and around the small vessels in advanced cases.

The *lymph nodes* of the abdomen and thorax are somewhat increased in size, but the superficial lymph nodes are not enlarged. In advanced cases the lymph nodes contain the typical large cells in abundance, considerable pigment, and a marked increase of connective tissue.

The *bone-marrow* shows irregular clusters of the same peculiar cells and pigment may be present in advanced cases.

Pathogenesis.—As to the nature and origin of the peculiar large cells found in the spleen, liver, lymph glands and bone-marrow, various views have been expressed. Formerly regarded variously as endothelioma, sarcoma, etc., it is now generally agreed that they do not represent a true neoplasm. Involving, as they do, the entire hemopoietic system, they would seem to originate *in situ* by hyperplasia of one or more elements of the constituent cells of the hemopoietic organs, stimulated by an unknown systemic poison. As to the particular cells from which they are derived, there is no complete agreement, but the tendency is toward the opinion that they are derived by proliferation from the endothelial cells, which they most resemble. Their origin, variously from reticular cells, leukocytes, pulp-cells and marrow cells, as well as from endothelial cells, has been suggested.

Clinical Features.—According to Brill and Mandlebaum, the diagnosis can be made from the clinical features alone. Formerly and, by some, still classified as a variety of splenic anemia, its unique pathology seems to justify its elimination from that conglomerate group. In general it strongly resembles splenic anemia, yet there are certain features that serve to differentiate it. It begins usually in early life, is probably congenital, and appears, as a rule, in more than one member of a family always in the same generation; it affects females compared with males in the proportion of 6 to 1, whereas splenic anemia preponderates strongly in males; its chronicity is far greater than in splenic anemia, with an average duration of more than nineteen years and a duration in one case of thirty-six years; the anemia, usually slight, is distinctly less a feature than in splenic anemia; the leukopenia, always present, is not so marked; the general health is less affected, often not at all; the spleen is much larger, as a rule; the liver, which enlarges later than the spleen, is regularly greatly enlarged in advanced cases, whereas in splenic anemia the enlargement of the liver, sometimes seen, is never marked; profuse and recurring gastric hemorrhage, a feature of splenic anemia, never occurs, although

epistaxis and oozing from the gums are common; jaundice has never been reported and ascites in only one case; a discoloration occurs on the exposed parts of the skin, in splenic anemia a more diffuse pigmentation is common; and finally a peculiar, brownish-yellow, wedge-shaped thickening of the conjunctivæ, appearing first on the nasal and later on the temporal halves of both eyes, occurs in all cases, according to Brill and Mandlebaum.

Besides splenic anemia, the literature contains a number of cases[1] of splenomegaly of varying pathology and ill-defined classification that have been confused with the Gaucher type.

Treatment.—Splenectomy has been performed in 8 of the 14 proved cases, with 3 operative deaths. Of the ultimate results too little has been published to warrant any conclusions.

KALA-AZAR. TROPICAL FEBRILE SPLENOMEGALY.[2]

(Leishmaniasis.)[3]

Introduction.—Since writing the article on Kala-azar for the first edition of this work, in 1907, the subject has been greatly amplified by an enormous literature on leishmaniasis and in particular on Infantile Kala-azar of the Mediterranean districts and on Oriental Sore (Dermal Leishmaniasis). The relation of Infantile Kala-azar and Oriental Sore, both of them leishmaniases, to Kala-azar of India is at present, 1914, the subject of so much controversy and active investigation that all three affections must be considered together in this place for an adequate presentation of the primary subject. However, in order to avoid confusion, the description in general will refer to Kala-azar of India, and all references to Infantile Kala-azar and Oriental Sore and their parasites will be clearly specified.

It may facilitate a clearer understanding to state the main problem that confronts us. Kala-azar of the Orient, Infantile Kala-azar of the Mediterranean district, and Oriental Sore are all caused by leishmania, to which, in the absence of proof of their identity, specific designations have been attached, namely, *Leishmania donovani* for the organism of Oriental Kala-azar, *Leishmania infantum* for that of Mediterranean Infantile Kala-azar, and *Leishmania tropica* for that of Oriental Sore. These separately named organisms, as found in human lesions and as grown in culture, appear to be essentially identical. The affections to which they give rise clinically are more or less distinct. Are the organisms one and the same or are they different varieties or species of a common

[1] See Brill and Mandlebaum, *Amer. Jour. Med. Sci.*, 1913, cxlvi, 878–880; and Ledingham, Allbutt and Rolleston's *System of Medicine*, 1909, v, 773–774.

[2] The subject of Kala-azar belongs properly to the Division of Infectious Diseases, but has been retained in this place because splenomegaly is the most striking objective sign, and in deference to past custom.—Editors.

[3] The most complete and satisfactory résumé of the entire subject of leishmaniasis and the full references to the literature by title will be found in the *Kala Azar Bulletin*, vol. i, No. 1, December, 1911; vol. i, No. 2, March 22, 1912; vol. (?), No. 3, July 11, 1912; and List of References, 1911, London Sleeping Sickness Bureau.

genus? If the organisms are identical, why the clinical differences? This states the problem presented for future solution, for its solution is not yet possible.

Synonyms.—Kala-azar (black fever), tropical febrile splenomegaly, Assam fever (from Assam, India), Dum-dum fever (from Dum-Dum, India), Burdwan fever (from Burdwan, India), Kala dunkh or Kala dukh, etc. The infantile type of Kala-azar in the Mediterranean district is usually called Infantile Kala-azar.

Definition.—A disease, endemic in certain tropical and subtropical countries in the Eastern Hemisphere and epidemic in parts of India, caused by a protozoal organism, *Leishmania donovani*, characterized by a chronic, irregular type of fever, marked splenomegaly, emaciation and cachexia, and terminating after several months or years in death from inanition or intercurrent infection, or in gradual recovery in a small minority of cases.

Geographical Distribution.—The disease is widespread in India, limited in the endemic form to its eastern half. It occurs in sporadic, endemic, and epidemic form in that country, where it has its strongest hold. It is found both in the larger cities, Calcutta, Madras, etc., and especially in the country districts. In Assam, India, it is widely distributed and exists in its worst epidemic form. Outside of India, the disease has been reported from China, Egypt, Arabia, and many countries bordering the Mediterranean. The Mediterranean cases are chiefly of the *infantile* variety. Occasional cases have occurred in Europe in persons invalided from the tropics. Only a single case has been reported from the Western Hemisphere, from Paraguay but originating in Brazil (Migone).

Dermal leishmaniasis (Oriental Sore) is widely distributed through the warm countries of the East and the Mediterranean district. In the Western Hemisphere it is common in South America (Brazil, Bolivia, Chili, Peru, the Guianas), a few cases have been reported from the Panama Canal Zone, and a form of the disease involving chiefly the ear is said to be widespread among the natives of Yucatan, Mexico, (Seidelin). The dermal affection of South America, commonly called "*Espundia*," differs clinically from Oriental Sore of the East, in particular in its tendency to oro-pharyngeal involvement, but no differences in the leishmania, morphological, cultural, or in the infection of animals, have been determined.

An apparent antagonism in distribution between Oriental Sore and Kala-azar has been recognized in India and other endemic centres. As a rule they do not occur together in the same districts. In India, Oriental Sore appears to be limited to the western and northern parts, whereas Kala-azar in its endemic form is limited to the eastern half of the country.

Etiology.—Discovery of the Parasite.—The parasite now accepted as the causal agent, *Leishmania donovani*, was first observed, November, 1900, by W. B. Leishman, at Netley, England, in Romanowsky-stained spleen smears made after necropsy on a soldier invalided for tropical splenomegaly from Dum-Dum, in Bengal, India. Leishman did not publish his observations until May, 1903, and believed that the parasite

found was a degenerate trypanosome. Donovan at once, July, 1903, confirmed Leishman's discovery by finding similar bodies in the spleen of patients dying from prolonged fever in Madras and also in fresh blood obtained by spleen puncture from a living patient affected with tropical splenomegaly. Many other observers soon added their confirmation of these findings.

In the meantime, in December, 1903, J. H. Wright, of Boston, published a description of bodies apparently identical with the Leishman bodies, found in the inflammatory tissue curetted from the base of an ulcer in a case of "Delhi sore" (Oriental Sore) in an immigrant child from Armenia. Wright's discovery of such parasites in Oriental Sore was soon widely confirmed. Wright proposed for the parasite of Oriental Sore the name, *Helcosoma tropicum*, but according to the rules of scientific nomenclature this designation has been changed to *Leishmania tropica.*

In 1904, Cathoire at Tunis observed for the first time certain bodies, which Laveran later identified as leishmania, in the spleen of an infant dying from anemia and splenomegaly (Infantile Kala-azar). This observation was subsequently confirmed widely through the Mediterranean region. The disease was found to be confined chiefly to infants and young children. The parasite, which has been designated *Leishmania infantum*, closely resembled that of Indian Kala-azar.

With the discovery, within a short period, of apparently identical parasites in Indian Kala-azar, Mediterranean Infantile Kala-azar and Oriental Sore, diseases differing considerably in their clinical aspects, the question of the identity of the parasite in all became paramount.

Nature of the Parasite.—Various views have been expressed as to the biological position of the parasite. Leishman believed that it represented a degenerated form of trypanosome; Laveran and Mesnil regarded it as a piroplasma and proposed the name *Piroplasma donovani;* Christophers thought it a spore stage of a microsporidium; Ross believed that it represented a new genus and proposed the name *Leishmania donovani*, from its discoverers; Rogers concluded that the organism belonged to the order *Herpetomonas* and proposed the name *Herpetomonas of Kala-azar;*

DESCRIPTION OF PLATE XXIII. (ROGERS.)

(*Magnification of all the figures* 1500 *diameters.*)

I.—Undeveloped Leishman-Donovan bodies from spleen-puncture film.
II.—Early stages of development, from two days' culture in acidified citrated blood: 1 and 2, body and macronucleus enlarged; 3 and 4, first appearance of eosin body; 5 and 6, elongation and subdivision; 7 and 8, first appearance of flagellum.
III.—Stages of division of the early flagellated forms.
IV.—Double, long, swimming forms.
V.—Fully developed, long, free, active single cells.
VI.—Degenerate forms.
VII.—Undeveloped forms in a white corpuscle.
VIII.—Early stages of development in a degenerating white corpuscle.
IX.—Stage in the formation of rosette.
X.—Separated flagella with micronuclei attached.
XI.—Rosette breaking up into free forms.
XII.—Small complete rosette.

PLATE XXIII

Schaudinn, Hartmann, and other authorities regarded it as a flagellate differing from any previously known form, of uncertain biological position, and, therefore, appropriately called *Leishmania donovani*, as suggested by Ross. As time has passed the tendency has grown to regard the organism as belonging to a new genus, *Leishmania*, and hence the specific designation of the parasite, *Leishmania donovani*. The similar (or identical) organism of Mediterranean Infantile Kala-azar has been designated *Leishmania infantum*, and the similar (or identical) organism of Oriental Sore, first named by Wright *Helcosoma tropicum*, has become *Leishmania tropica*.

Distribution of the Parasite in the Body.—Leishmania in Kala-azar are found most numerously in the spleen, liver, and bone-marrow, but also in the lymph glands, kidney, brain, intestinal ulcers, inflammatory effusions—in fact, in most of the organs. They have not been found in the urine or feces, except in fecal mucus in a single case of Infantile Kala-azar (Cretien). The parasites are found sometimes free but more commonly enclosed in swollen endothelial cells or macrophages or among cell detritus. Donovan found them in the peripheral blood in 75 per cent., and Patton in a larger percentage of selected advanced cases of kala-azar in India.

Description of the Parasite.—The parasite, as found in the human body, stained by the Romanowsky stain or one of its modifications, is seen as a small, sharply defined, generally round or oval, sometimes oat-shaped body, about the size of a blood platelet (2 to 4μ in diameter), with faintly stained protoplasm and two characteristic chromatin masses which are clearly brought out by the stain as lilac-colored bodies, usually placed at the opposite sides of the lesser diameter of the parasite. The larger mass, the macronucleus, has a variable shape, generally round or oval, and is placed at one side of the parasite at its periphery. The much smaller micronucleus is generally rod-shaped or round, much more deeply stained than the macronucleus and placed near the other side of the parasite. The parasites in smears from the spleen or liver may be seen in enormous numbers contained in macrophages or lying in a matrix of cell detritus. In advanced cases the parasites may also be found within leukocytes in the peripheral blood. (See Plate XXIII.)

Cultivation of the Parasite.—In 1904, Leonard Rogers succeeded in cultivating the parasite outside the human body in infected blood, obtained by spleen puncture from Indian Kala-azar patients, to which was added normal salt solution and weak sodium citrate solution. He subsequently modified this medium by adding citric acid to the point of faint acidity. In this medium, kept free from bacterial contamination and at an optimum temperature of 20° to 22° C., the Leishman bodies rapidly multiplied and in three or four days passed through a series of developmental stages, briefly described as longitudinal division, enlargement and final evolution of flagellated, actively motile, elongated forms, which were arranged circularly in large rosettes with the single flagellum of each individual directed inwardly toward the centre of the group. The fully developed organism was a long, oat-shaped body, with the larger macronucleus near its centre, the small, rod-shaped micronucleus at one end surrounded by a round, clear, eosin-staining body, and a

single flagellum springing apparently from this eosin body, but in reality from the micronucleus. The flagellum was long and slender and showed no trace of an undulating membrane. The parasite was grown between 15° and 25° C., best at about 22° C., and was quickly destroyed by accidental bacterial contamination.

In 1908, Nicolle introduced an improved culture medium, a modification of the original Novy-McNeal medium. The Novy-McNeal-Nicolle medium, commonly referred to as the N.N.N. medium,[1] is the one now generally used. In this medium full development to flagellated forms takes place with *L. donovani, L. infantum, L. tropica* and leishmania in general, but certain minor differences in the facility of growth of leishmania of different origin have been noted on the different media in use. In the N.N.N. medium subcultures can be produced indefinitely.

Relation of Insects.—*Bedbugs, fleas, mosquitoes.*—Patton (1906-07), in Madras, by feeding the native bedbug, *Cimex rotundatus,* on spleen blood from Kala-azar patients, claimed to have succeeded in obtaining the full development of the parasite in the bedbug's stomach cavity, as already obtained by Rogers in artificial blood medium. Patton's success with bedbugs proved complete only when he conducted his experiments in the cooler winter months with a temperature which Rogers had found necessary to the successful cultivation of the parasite. It may be added that Rogers had previously suspected the bed-bug as the carrier of the disease.

Patton, renewing his studies in India, in 1912, reported complete success in infecting both the Eastern type of bedbug, *Cimex rotundatus,* and the European or Western type, *Cimex lectularius,* by feeding them on the blood of a case of Kala-azar. The full development to flagellated and post-flagellated forms was obtained. It was further found that the flagellating forms were promptly destroyed by permitting subsequent feedings, a single feeding being required for the perfect development of the parasite in the bugs. This fact was thought to explain previous failures by other workers and to suggest a reason for the tendency of the disease not readily to spread outside endemic areas.

The only confirmation up to the present (1914) of Patton's success in infecting bedbugs appears to be by Wenyon (1911) and by Patton himself (1912) both of whom reported successful infection of bedbugs with *Leishmania tropica* from cases of Oriental Sore. All attempts to transfer the infection from infected bedbugs to animals have failed.

Basile and others (1909+) claim to have successfully infected fleas (*Pulex irritans* and *Ctenocephalus canis*) with *Leishmania infantum* with full development of the parasite into flagellated forms in the gut and further to have *transferred the infection to dogs by the bite of the infected fleas.*

Franchini and others (1911+) claim that *L. donovani, L. infantum* and *L. tropica* can all develop to full flagellation in mosquitoes (*Anopheles maculipennis, Stegomyia fasciata*).

[1] For formula, see Nicolle, *Ann. de l'Inst. Pasteur,* May, 1909, xxiii, No. 5, 361; also abstracted in *Kala Azar Bulletin,* London, December, 1911, i, No. 1, pp. 56–57. For Row's newer modification of the N.N.N. medium, see *Brit. Med. Jour.,* 1912, i, 1119.

The real bearing of all these claims on the question of the natural intermediate host of the parasite can only be decided by far more exacting proof than has hitherto been adduced. Most of the claims made are open to serious question.[1]

Occurrence in Animals.—Nicolle and Comte, in Tunis, in 1908, first demonstrated that dogs suffer from a natural infection of leishmania that appeared to be identical with *L. infantum* in Infantile Kala-azar. Since it has been found that dogs are subject to natural leishmaniasis in nearly all endemic centres of Kala-azar except India. In Madras, an endemic centre, Patton failed to find leishmania in a single instance among 1321 dogs examined. A single case of natural infection in a cat has been reported. Dogs and camels suffer with a form of dermal leishmaniasis, closely resembling Oriental Sore.

Animal Inoculation.—Nicolle, in 1908, was the first to successfully infect dogs and later monkeys with the parasite from Infantile Kala-azar. Since then several other animals have been infected from Infantile Kala-azar, but dogs and monkeys are the only animals that have been readily inoculated. All the early attempts to infect dogs by inoculation from cases of Indian Kala-azar failed and this failure has been emphasized as evidence of a specific difference between *L. donovani* and *L. infantum*. But this point of difference has recently fallen, as Donovan and Patton (1913) have succeeded in infecting dogs, jackals and monkeys from cases of Indian Kala-azar and Weynon also has infected dogs. Row (1912), has also succeeded in producing by cutaneous and subcutaneous inoculation in monkeys local nodules containing the parasite, *L. donovani*. Oriental sore is readily inoculated into dogs and monkeys, as well as human beings.

Contributing Factors in Etiology.—*Climate.*—The disease is found only in warm countries, except for occasional imported cases. Rogers thinks it highly probable that infection and the onset of the disease occur chiefly during the cooler months of the year in India, *i. e.*, November to April, although the frequently long incubation period may delay the onset of symptoms to any period of the year. Tending to support this view are the facts that Rogers succeeded in cultivating the organism only at a range of temperature, 60° to 75° F., which is commonly found in India during the cold season, and that Patton's feeding experiments with bedbugs in Madras were fully successful only at this period of the year. In extending up the Assam Valley, the disease was always checked as it approached the high elevations. where the weather was too cold. There is no indication of relation to moisture or rainfall.

Sex and Age.—There is no difference in the sex incidence. Cases in husband and wife are common. Childhood is the age of predilection and thereafter each succeeding decade of life shows a steadily decreasing incidence; 20 to 40 per cent. of all cases occur under the age of ten years, 50 to 70 per cent. under the age of twenty years; after forty years the disease is relatively infrequent. The Infantile Kala-azar of the Mediterrancan countries occurs almost exclusively in infants and young children

[1] For a criticism of these claims see Fantham, *Brit. Med. Jour.*, 1912, ii, 1196.

chiefly before the fourth year, although occasional cases in adolescence and rare cases in adult life have been noted.

Race.—In India the disease is largely confined to the natives, although sporadic cases in Europeans in Calcutta and other cities are not very uncommon. According to Rogers, of 87 such cases in Europeans over 87 per cent. were born and bred in India and only about 13 per cent. were immigrants from Europe. Foreigners attacked belong almost invariably to the lower classes and live in the native quarters, although, of course, exceptions occur.

Transmission.—All the evidence points clearly to the transmission of the disease by intimate personal contact with infected persons and especially by sleeping in infected houses, which account for the vast majority of cases. Europeans have been known to acquire the disease by cohabiting with infected native women, even in certain instances, when the native women have visited the quarters of the Europeans. A single night of such cohabitation has been followed by infection in the exposed foreigner (Rogers). This would prove that the active agent of infection can be carried on the person or clothing of those harboring the disease. Casual relations with such people seem to be practically free from danger, although, perhaps, not entirely so, if the bedbug is proved to be the inoculator of the parasite. The slow progress of the disease from house to house and along the lines of communication can, in almost all instances, be traced to direct contact with infected persons.

Pathology.—The *skin* is muddy and often shows varying degrees of diffuse or irregular pigmentation which may extend to the mucous membrane of the mouth. Moderate icterus may be found in some cases, generally associated with cirrhosis of the liver.

The *spleen* is invariably greatly enlarged, pigmented, firm and friable, but not sclerotic, as a rule. Its substance is crowded with innumerable Leishman bodies filling the interior of the swollen cells and scattered loose in the lymph and blood spaces mingled with cell detritus. Infarcts occur occasionally and perisplenitis with adhesions is common.

The *liver* is enlarged, often enormous, firm and friable, pigmented, and contains an excess of iron. The parasites may be present in enormous number, contained apparently in the swollen endothelial cells of the capillaries and lymph channels or lying among the detritus of such degenerated cells. The parenchyma cells of the liver, although often extensively degenerated, are not invaded by the parasite. The centres of the lobules are marked with a whitish deposit, consisting of masses of parasites enclosed in endothelial cells or scattered among the cell detritus. Cirrhosis of the liver is common, usually intralobular, sometimes, also, of the perilobular or portal type.

The *bone-marrow* is loaded with parasites contained in macrophages and, also, scantily in leukocytes and myelocytes.

Otherwise, the morbid anatomy is that common to all diseases associated with wasting, anemia, and cachexia, namely, fatty degeneration of the organs, œdema, effusions in the serous cavities, hemorrhages, etc. The pathology is further amplified by that of various complications, which, in the majority of cases, are the direct cause of death, especially dysentery, cancrum oris, pneumonia, meningitis, pericarditis, septicemia, etc.

Clinical Picture, Symptoms, and Course.—The disease commences with high fever, often preceded by a rigor or chill, and sometimes by vomiting and headache. The fever of onset varies in type, being most commonly remittent or sub-continued, less frequently intermittent. According to Rogers, the early remittent fever is often specially characterized by a daily double or sometimes triple rise for several days without treatment. These variations in the daily temperature of the early fever are thought to be of importance in helping to differentiate Kala-azar from typhoid fever, with which it is likely to be confused in sporadic cases. The pulse is accelerated somewhat more than in typhoid fever. In other cases the fever of onset is of a low, continued type, with slight daily variations, or it may be intermittent. The original fever lasts usually two to six weeks or longer, during which the spleen enlarges rapidly and, perhaps, also, the liver to a slight extent. A period of apyrexia follows the original fever, accompanied by improvement, which in turn is succeeded by a second period of fever, and thus periods of pyrexia and apyrexia of varying length alternate as the disease progresses. The secondary accessions of fever show marked variation in type, remittent and intermittent forms often alternating over long periods, with spells of apyrexia interspersed, until finally in many cases a low type of intermittent or continued fever develops and persists for months.

During the periods of pyrexia, especially the remittent fever, the patient rapidly grows anemic, wastes, and has great enlargement of the spleen and moderate enlargement of the liver, with tenderness over these organs. With the enlargement of the spleen and liver and the emaciation and cachexia, the patient presents a striking picture of a pot-bellied skeleton.

Among the common minor symptoms may be mentioned delirium, severe headache, usually frontal, neuritic pains, pains and swelling over the joints, slight œdema of the extremities, vomiting, diarrhœa, wasting and loss of the hair, petechial eruptions, epistaxis, hemorrhages from the gums, etc. Dysenteric symptoms—bloody, mucous stools—occur especially frequently, and are almost the rule in advanced cases.

The Mediterranean infantile type of Kala-azar does not differ materially from that of India except in respect to the age incidence.

Cutaneous Symptoms.—In advanced cases the skin is sallow or earthy, often with a moderate, diffuse or patchy, grayish pigmentation, which may also involve the buccal mucous membrane. The darkness of the skin (Kala-azar; black fever) is not usually extreme, often slight. The expression of the face is heavy and lethargic. Icterus, secondary to cirrhosis of the liver, is not uncommon late in the disease. Petechiæ in the skin are frequent. Œdema of the extremities may occur with anemia or associated with cirrhosis of the liver. Night-sweats, following the common afternoon exacerbations of temperature, may be a marked feature. Pains and swellings near the joints occurring early in the disease, with fever and sweats, often lead to a diagnosis of rheumatism.

Spleen.—This is invariably enlarged, being appreciable in the early stages of the fever as a soft spleen tumor and rapidly increasing in size and firmness during the subsequent febrile attacks. The spleen reaches

the navel in 60 to 80 per cent. of cases and the anterior superior spine of the ilium in from 10 to 20 per cent. It is rarely found less than a hand's breadth below the costal margin. During the periods of apyrexia and especially during the prolonged postfebrile period, often occurring late in the course of the disease, the spleen tumor may undergo marked reduction. Dragging pains over the enlarged organ are complained of, or pain of a more severe character in case of infarct or perisplenitis.

Liver.—This usually enlarges with the spleen, but later and to a less degree. After several months it may occasionally reach the navel and in rare cases is even larger than the spleen. Symptoms of cirrhosis with portal and biliary obstruction, *i. e.*, icterus, ascites, gastro-enteric disturbances, etc., are not infrequent late in the disease. Perihepatitis with adhesions may lead to tenderness and pain.

Blood.—This shows a secondary type of anemia which seldom reaches an extreme grade except from complications. Loss of red corpuscles to 2,500,000 per cmm. and of hemoglobin to 35 to 40 per cent. in advanced cases is the rule. Occasional normoblasts occur. Poikilocytosis and polychromatophilia are unusual except in the last stage. The leukocytes are never increased in uncomplicated cases, except in rare instances in Infantile Kala-azar of the Mediterranean district. A pronounced leukopenia is the rule, not infrequently to 1000 or less per cmm. This is further characterized by a constant and marked relative increase of the lymphocytes and large mononuclears with a corresponding reduction in the polymorphonuclear neutrophiles. The eosinophiles may be considerably increased in certain cases, probably due to concurrent ankylostomiasis and other causes. As already stated, leishmania may be found within the leukocytes, usually the polynuclears, in advanced cases. The platelets are increased in number.

Urine.—The urine may show traces of albumin, perhaps occasional casts, a deposit of phosphates, and sometimes it is high-colored from red corpuscles. Parasites are not found in the urine.

Duration.—This is from six to nine months on the average, but may cover a period of two or three or more years, ending in the great majority of cases in death, which may occur at any period of the disease with exacerbation of fever, but usually results from inanition complicated with some terminal infection. The Mediterranean infantile type of the disease tends to last longer than the Indian type.

Complications.—As seen in India, Kala-azar is frequently complicated by such common diseases as malaria, ankylostomiasis, dysentery, etc., and is usually brought to its fatal termination by some inflammatory complication. In 40 autopsies made by Rogers, all but 7 showed complicating infections or local conditions contributing toward death, as follows: pneumonia, 11; dysentery, 10; cancrum oris, 7; pneumococcus meningitis, 2; purpura, 2; cerebral hemorrhage, 2; pulmonary tuberculosis, 2; pericarditis, 1.

Diagnosis.—The disease occurs in India in sporadic, endemic, and epidemic form. The sporadic cases are the ones most liable to be encountered by physicians in the tropics and are the cases that are most likely to go to the autopsy-room for diagnosis. The diagnosis is made certain only by finding the parasites, for which purpose thorough and repeated

blood examinations should be made. If blood examination prove negative, spleen or liver puncture may be resorted to in selected cases and will prove positive for the parasites in most cases at all stages. A rather small needle should be used and need not be introduced deeply into the organ. The few drops of contents should be spread on several coverslips, stained by some form of the Romanowsky stain, and examined with an oil-immersion lens. In view of possible fatal hemorrhage following spleen puncture, this procedure should not be too lightly undertaken. Special contra-indications to its employment are marked anemia, asthenia, and a hemorrhagic tendency, with increased coagulation time of the blood. Calcium chloride or lactate may be administered before and after the puncture, to increase the coagulability of the blood and reduce the danger of hemorrhage. It is advisable also to reduce the movements of the spleen in abdominal respiration by adjusting a tight abdominal bandage during and after the operation and keeping the patient at rest in bed until all danger is past. Puncture of the liver may be resorted to successfully and with less danger of fatal hemorrhage.

Wenyon has obtained positive cultures on N.N.N. medium from the spleen blood in dogs when parasites could not be found in smears or at autopsy. The same method could be applied to human cases for diagnosis. Wenyon and Mayer (1914) have obtained positive cultures on N.N.N. medium from the finger blood of Indian cases. Cochrane in China excised the small superficial lymph nodes for making smears and in all seven cases found leishmania readily. Specific agglutinins may be present in the blood in Infantile Kala-azar but in such minimal amounts as to be valueless for diagnosis (Caronia).

Differential Diagnosis.—The diseases most commonly confused with Kala-azar are typhoid fever, malarial fever, Malta fever, ankylostomiasis, leukemia, splenic anemia, and other forms of splenomegaly. The malarial fevers are excluded by the continued absence of malarial parasites in the blood and by the quinine test; ankylostomiasis by negative examinations of the stools for the ankylostoma and by thymol treatment; leukemia by the absence of its well-known blood picture; splenic anemia by the irregular fever and the finding of leishmania; typhoid fever by the absence of the Widal reaction, negative blood cultures and the subsequent course; Malta fever by the absence of agglutination with cultures of *Micrococcus militensis*, etc.

Prognosis.—This is briefly summarized by the mortality figures, 96 to 98 per cent., in both the Oriental and the Mediterranean varieties.

Prophylaxis.—With the parasite known and bedbugs, fleas and mosquitoes incriminated as possible vectors of infection, as well as from the observations by Bentley, Price, Rogers and others on the successful control of the disease by measures of segregation, at least some of the possible means of prevention are indicated. Rigid quarantine against infected individuals, houses, and localities should be enforced. Foreigners in endemic centres should be warned of the danger of association with the natives. The disease seems to be communicated only by the most intimate contact with infected persons or dwellings, especially by sleeping with such persons or in their houses. Casual relations with infected natives seem almost free from danger.

Treatment.—The terrible mortality tells its own mournful story of therapeutic impotence. Quinine, alone, may be found of value, although by many of the most experienced physicians, who have had unusual opportunity for studying its effect in India, it has been discarded as worthless. Rogers is conspicuous by his insistence on the efficacy of this drug. He uses it in large doses, gradually increased to 60 and sometimes to 90 grains per day, and continued in these large doses for weeks and, if necessary, for months. He claims that the high remittent fever is reduced and slowly assumes a low, continued, benign form which in favorable cases gradually exhausts itself and is followed by apyrexia and improvement. After the apyrexia has lasted several months, complete recovery is the rule and relapses are exceptional. As soon as the temperature has fallen to the low continued or intermittent type under the use of such large doses of quinine, Rogers reduces the dose to about 20 grains daily, which is sufficient to keep the temperature from returning to its previous level. This method of treatment was systematically employed by Price in 500 consecutive cases with permanent recovery in 25 per cent., contrasted with recovery in only 4 per cent. of several hundred cases previously treated by the same physician in which the quinine treatment was not so vigorously and systematically used.

Muir[1] claims to have cured almost every case of Indian Kala-azar, among numerous cases during a period of three years, in which treatment was begun within the first three months of illness and persisted with for a sufficient period by the hypodermic or intramuscular injection of quinine (formula: quinine sulphate, gr. xxxii; dilute sulphuric acid, ℥j; distilled water, ℥iv). As the injection of this solution is painful, it is preceded by an injection through the same needle of 5 minims of a 2 per cent. solution of cocaine. A painless effusion results from the injection of the quinine solution when given in sufficient amount, which should be from 20 to 90 minims. Subsequent injections should be given as soon as or just before the effusion has disappeared. A marked increase of polynuclear leukocytes of the blood follows such injection and is thought to be concerned in the process of cure. With the increase of polynuclear cells there is reduction in size of the spleen and liver, the temperature becomes normal and the patient gains in weight.

The newer arsenical compounds (atoxyl, salvarsan, etc.) have been widely tried in Kala-azar but the reports are not encouraging. On the other hand, in Oriental Sore the intravenous use of salvarsan has led Peterson to conclude that it acts almost as a specific. Row has reported the use of a vaccine, a glycerinated dead culture of *L. tropica*, in three cases of Oriental Sore, with prompt healing. The use of similar vaccines in Kala-azar has given no results.

Needless to add, tonics, such as iron and arsenic, and careful attention to the patient's general care should be suitably employed. Complications must be treated as they arise. Malaria and ankylostomiasis, which are common complications in India, can be suppressed, respectively, by quinine and thymol. Improvement and even complete recovery in rare cases have followed various intercurrent septic infections.

[1] *Indian Med. Gaz.*, 1911, xlvi, No. 2, 58.

PART V.

VASOMOTOR AND TROPHIC DISORDERS.

CHAPTER XXVI.

RAYNAUD'S DISEASE.

By Sir WILLIAM OSLER, Bart., M.D., F.R.S.

Definition.—A vascular change, without organic disease of the vessels, chiefly seen in the extremities, but also occurring in the internal parts, in which a persistent ischemia or a passive hyperemia leads to disturbance of function or to loss of vitality with necrosis of the parts. This definition excludes the cases of necrosis due to obliterative arteritis, and the cases of postfebrile and of multiple neurotic skin gangrene.

Introduction.—The blood supply of all parts is controlled by the vasomotor mechanism, which regulates the amount by varying the calibre of the arteries. The sudden blush of shame, the instantaneous pallor of fear, indicate the extraordinary rapidity of action, and illustrate, moreover, the extremes of vascularity in the skin. The regional control of the circulation is analogous to that of a central distributing station in a great irrigation system, with its elaborate system of telephones to and from all the plantations. A uniform supply may be given to all, or the various streams may be diverted to a supplementary reservoir; any local plantation may be flooded at a moment's notice, or the supply may be cut off to the finest rivulets.

In the skin, one of the most vascular of parts, the blood supply varies greatly in health, particularly in the degree of normal distension of the vessels of the exposed parts. Whole nations are pallid, others are rubicund. There is an antagonism between the amount of pigment and the degree of permanent distension of the vessels of the skin. The darker Latin races have not nearly the same rich blood supply to the face and hands as the fair Teutonic people. How rarely one sees in France or Italy the full complexion of the English. In individuals heredity and constitutional peculiarities have an important influence on the cutaneous blood supply; occupation, too, is a factor of the first moment, as persons who constantly work in the open air have a permanently heightened skin vascularity. As is well known, the grade of the vascularity is no indication of the amount of blood in the body—there may be anemia with a red face, and a chronic pallor may be present with a normal blood

count. Many individuals have what may be called an unstable skin circulation—the vasomotor mechanism is not under good control, but works badly, so far as the skin is concerned; that special plantation, to use again the analogy of the central irrigation scheme, is too apt to be flooded, or the supply may be cut off abruptly. How many persons, healthy enough in other respects, are constantly worried by an abnormal filling of the vessels of the face, sometimes permanently, but more often intermittently, the result of central, emotional causes.

By far the most common vascular skin reaction is to cold, in which we see four phenomena of the first importance in the study of Raynaud's disease. A hand exposed to a very low temperature is at first flushed, then blue, and finally grows pale; the radial artery may be felt to get small and the pulse more and more feeble. At first the anemia may be patchy, as though some capillary areas had greater resistance, but soon the hand is of a dead white color, less sensitive than normal, and stiff from inability of the muscles to move freely. This bloodless condition, due to spastic contraction of all the vessels, is called *local syncope.* Continued exposure at a very low temperature may result in a freezing of the whole hand. Brought into the warmth, the blood gradually returns to the parts, a backward flow takes place from the veins, as a hand which has been frozen may become gorged with venous blood before a radial pulse is perceptible. It grows livid, mottled, and swollen; pressure with the finger causes a spot of anemia, but the return flow is sluggish and almost imperceptible. Pain begins at this stage—the stage of *local asphyxia.* If the hand has not been exposed for a very long period this venous stasis gradually disappears. The radial pulse begins to be more distinct, the lividity is less intense, and the finger imprint is more quickly obliterated. Soon the fingers begin to throb, and the whole hand aches, and within half an hour or less the color is a vivid pink, the arteries are throbbing and large, and a pulse may be felt in every finger, and the capillary pulse is visible in the nails—this is the stage of *active hyperemia.* But if the hand has been exposed for a very long time and frozen hard, the venous stasis which follows the thawing does not disappear, the fingers remain livid and cold, the circulation does not become reëstablished, and *necrosis* or *gangrene results.*

In Raynaud's disease these four phenomena of frostbite, singly or together, are experienced *without frost,* sometimes, indeed, as a result of exposure to cold, but more frequently due to unknown internal causes, which bring about precisely similar vascular reactions in the fingers or toes, ears, and nose. In a majority of healthy persons the vasomotor mechanism works very smoothly and the reactions are within narrow limits; but many people have naturally, or acquire, a great instability of this system, so that abnormal reactions follow slight stimuli. S. Solis Cohen has called this condition vasomotor ataxia, and it is just in these individuals with an imperfect control of their irrigation pipes that we see the phenomena of Raynaud's disease. The morbid flushing and blushing, the vascular erythism of Basedow's disease, the transitory erythemas of the neurasthenic, the arterial spasm in migraine, in certain types of angina pectoris, and possibly the vascular crises in many abdom-

inal conditions (lead colic, tabes, angioneurotic œdema, etc.) all come under this vasomotor ataxia, either of the dilator (paralytic) or constrictor type. A scratch with the finger nail, a line drawn, say, on the skin of the chest or abdomen, is followed by a very slight reaction, usually a fine red line, but in the subjects of vasomotor instability one of three reactions follows; the most common is an intense hyperemia on either side of the line, 4 or 5 mm. or more in width, which lasts for ten or more minutes, and is sometimes associated with a widespread erythema of the adjacent skin. This is the characteristic vasodilator reaction, and is always an active, never a passive, hyperemia. Much less common is it to see, following the irritation, a white line, a band of anemia 4 or 5 mm. in width, which results from spasm, vasoconstriction, of the small arterioles of the skin. It may disappear gradually or it may be followed by an active hyperemia. These two reactions, dilator and constrictor, represent the two vascular skin reflexes, which are as important to test as the knee reflex, as they give an indication of the existence, degree, and type of vasomotor ataxia. The third and rarest reaction is the exudative, when in the line of the irritation, serum is poured out from the hyperemic vessels with the production of a wheal, factitious urticaria (dematographia).

Etiology.—It is not a common disease. Among 23,000 medical patients admitted to the Johns Hopkins Hospital in a period of about twenty years there were only 19 cases. Cassirer collected 168 cases from the literature for his monograph (1901) and Monro 180 cases for his work (1899). The last-named author estimates that about 1 case occurs among 3000 patients.

Nationality.—The disease appears to be more common in England and France than in Germany. It is not rare in America, as our figures show. It is relatively more frequent among Hebrews.

Sex.—Women are much more frequently affected than men—62.5 to 37.5 per cent. in Monro's series—and this holds good for both mild and severe forms.

Age.—More than 60 per cent. of the cases occur between the tenth and the thirtieth year. In Cassirer's statistics there were 22 cases under five years of age; from five to ten, 8; from eleven to twenty, 25; from twenty-one to thirty, 40; from thirty-one to forty, 27; from forty-one to fifty, 28; above sixty, 18. Friedel saw a six months' old child attacked with swelling of the back of the hand; gradually the fingers of both hands became blue and necrosis of the tips of several of the terminal phalanges occurred (Cassirer). True Raynaud's disease is rare in the aged, and some of the cases reported have been senile gangrene from endarteritis.

Family Disposition.—Several members of the family may be affected. In the milder forms it is not uncommon to see dead fingers in three or four sisters. I know one family in which the mother when young had recurring attacks of "white and blue fingers," and her three daughters have been greatly annoyed with vasomotor disturbances of the hands and feet. In Colman and Taylor's patient the grandfather and the great uncle had Raynaud's disease. Cases of symmetrical gangrene have been reported in sisters (Makins) and in three brothers (Bramann).

Psychical Disturbances.—To a sudden shock, or a fright, the symptoms have been assigned. Nervous, highly strung individuals are certainly more prone to the disease. Some of the worst cases have been in hysterical patients.

Sexual disturbances were thought by Raynaud to play an important part. In some patients mild attacks have been more likely to come on at the menstrual period. In one instance the disease followed directly upon pregnancy (Dickinson). Sexual excesses have been thought to be of moment.

Cold and Damp.—The milder forms are much influenced by climate and by the weather. Cases of local asphyxia are much less common in America than in England, where severe chilblains leading to superficial necrosis represent a frequent type of the disease. Cold has an important influence, and there are cases in which the symptoms occur only in the winter, and, as a rule, patients liable to attacks are always worse in cold weather. On the other hand, a patient of Raynaud's was always worse in the summer. Washing the hands in very cold or in very warm water may bring on an attack.

But in a considerable number of the cases no factor of any moment can be determined—the disease begins in healthy individuals, and the actual cause remains obscure; in a majority, however, there is a marked neuropathic disposition, an instability of the nervous system, or an actual perversion as in the hysterical cases.

Infectious Diseases.—In many acute and in a few chronic infections multiple gangrene occurs, but it is of a different type to that of Raynaud's diseases and should not be included in this category. In malaria, typhoid fever, measles, and scarlet fever local areas of necrosis may occur in various parts of the skin; in a few cases acrocyanosis has preceded the local gangrene of the finger tips, but, as a rule, the distribution is very different, the skin of the trunk or of the limbs, the lips, and the cheeks. In syphilis true Raynaud's disease may occur, but many of the cases of gangrene in the affection are due to arteritis. A remarkable case of Raynaud's disease in congenital syphilis is quoted by Cassirer.

Arteriosclerosis.—Vessels beginning to be diseased seem particularly prone to spasm, and a certain proportion of cases of true Raynaud's disease show widespread arterial changes, but a sharp distinction should be drawn, when possible, between the local gangrene due to obliterative arteritis and that which follows the protracted asphyxia of Raynaud's disease.

Nervous Diseases.—Gangrene occurs in a whole series of organic affections of the nervous system—neuritis, many affections of the spinal cord, acute and chronic, and in hemiplegia. These various forms of local gangrene, some of which bear a striking resemblance to Raynaud's disease, will be discussed in the section on diagnosis.

Morbid Anatomy and Pathology.—No characteristic changes have been found. Cassirer concludes that we have not, as yet, any sufficiently thorough study of all the parts in a typical case. Not one of the negative cases has been of such a typical nature, nor has the examination been of so exhaustive a character as to justify the statement that there is no

anatomical basis in the disease. The positive results consist either of changes in the bloodvessels or in the nervous system, singly or combined, but none of these are in any way peculiar or constant. Neuritis has been found in several very carefully studied cases but it is impossible to say whether it was causal or a complication of the disease itself. Changes in the cord have been reported, but the cases have not always been genuine instances of Raynaud's disease. Endarteritis has been found in some genuine instances of long standing, in others the vasomotor changes have been due to the chronic disease of the arteries, and the cases do not come in the category of Raynaud's disease. Endarteritis, endophlebitis, and degeneration of the nerves have been found. And lastly, the examination has been negative in a number of carefully studied cases.

The *pathology* lends itself to theoretical discussion. The key to it is found in study of the effects of cold in the vascular system. The mild and severe types correspond to chilblains and frostbite. Every feature of the disease is mimicked by the effect of cold in the extremities, and we know cold itself is one of the potent factors in inducing the recurring attacks. We have already noted the sequence of vascular events when a part is exposed for a long time to a low temperature, the vasoconstrictor effect on the arteries, capillaries, and veins producing local syncope, which may itself pass into necrosis; but more commonly a vascular reaction takes place, the blood flows back from the veins, and a state of asphyxia or cyanosis follows. From this, one of two events may result: if the part has not been long exposed, as the tip of the nose or an ear in ordinary mild frostbite, the asphyxia gradually disappears, the arteries begin to dilate, the parts get red, and a state of intense hyperemia follows, with pain and throbbing, and no necrosis results; on the other hand, if the part has been exposed for a long time, no vascular reaction takes place, the local cyanosis remains, the circulation is not reëstablished, and necrosis or gangrene results. We have seen that constrictor and dilator influences pass from the controlling centres to every vascular territory of the body, and they may be excited by mental, external, or somatic stimuli. There are persons in whom the centres controlling these vasomotor actions are unstable—the machinery of the irrigation centre is in charge of an inexperienced official who has not learned to work the sluices in proper response to the telephonic demands; he turns a full head of water into one of Mr. Epidermis' farms and forgets all about it, or he shuts off the supply from another, flooding the one, parching the other, and unless a call gets through in time to correct the mistake, death of the crops is the result. This is exactly what happens in Raynaud's disease. The centres are at fault and work imperfectly. The reaction to external cutaneous stimuli is very varied, usually vasodilator but often vasoconstrictor, which is the more important of the two in Raynaud's disease.

One cannot predict in an individual case when the skin is irritated whether the response will be constrictor or dilator. It has been suggested that when the *white line* of anemia follows there is disturbance in the suprarenal metabolism, but of this there is no evidence, and a prolonged study has convinced me that its only indication is a morbid sensitiveness

of the vasomotor centres. In the local syncope of a finger or of the hand widespread constrictor influences pass to the subsidiary centres, controlling the circulation of the part, and the arteries, capillaries, venules, and veins are thrown into a state of spasm. The contraction of the arteries may be felt (in the radial) and seen (in the retinal arteries); the spasm of the veins may be seen and has been observed by Barlow and others in cases of Raynaud's disease. The spasm of the capillaries is probably a sort of "squeeze" on the part of the bloodless tissues, and possibly the muscle fibres of the skin itself may be affected. The dead white, cold finger contains not a drop of blood, and is as exsanguine as if a small Esmarch bandage had been applied. Suddenly the sluice gates are opened and there is a rush of fluid into the empty channels, every stream is full, every pipe gorged to bursting. When you take off the Esmarch bandage from a finger, so rapid is the inundation that the eye can scarcely follow it. And this is what happens when the local syncope gives place to the active hyperemia. The flushing is rarely so sudden, but a dead white finger may become hyperemic in from twenty to thirty seconds. The ischemia and the active hyperemia are readily explained—we see them every day as the effect of constrictor and dilator influences.

The *local asphyxia* is another matter. In frostbite, active hyperemia, cyanosis, syncope is the order; the cyanosis follows a transient flush of hyperemia seen as the first reaction to the cold. In Raynaud's disease the order is usually syncope, asphyxia, hyperemia. In frostbite it seems clear that the asphyxia is due to a backward flow from the veins, to which the local syncope yields as the part thaws, before the arteries passing to the part can be felt to pulsate. The asphyxia of Raynaud's disease may be due to the same cause; contraction of the veins has been seen by Barlow and by Weiss, but that was when the asphyxia already existed. But the first thing must be the relaxation of the spasm of the venules and veins to permit of the blood entering the empty capillaries. The stasis and cyanosis persist so long as the arterioles and arteries remain in spasm. In moderate grades of asphyxia some little blood trickles through, but in the deep purple skin of a typical example of Raynaud's disease the circulation has ceased and death of the part is imminent. The necrosis is a simple matter, as simple as if a string is tied tightly about the finger tip.

The cause of this instability of the vasomotor centres, the nature of the change in them, the reason of the symmetrical distribution, an explanation of the associated hemoglobinuria—these are questions awaiting solution. With a clear-cut symptomatology, having affinities with other affections due to angiospasm, the disease must not be confounded with a series of other disorders which have with it gangrene as the most striking feature.

Symptoms.—*General Description.*—There are *mild, moderate,* and *severe types.*

(*a*) **Mild Forms** (*formes frustes*).—A girl, aged seventeen or eighteen years, subject, perhaps for years, to cold hands and cold feet, begins to have tingling in the fingers and toes, and finds that on exposure, or when the weather is cold, her hands and feet get very blue. When she comes into

the house they throb and ache, get red and hyperemic, and feel tense and swollen. It may take hours before they are normal. During successive winters these symptoms may be repeated, and the condition is regarded, and rightly so, as chilblains. There is nothing to distinguish it from scores of cases of this common affection, but one day, following perhaps a longer exposure to cold or after a week or two of cold weather, in which she has had to work in a cold room, the cyanosis is more persistent, the skin over the knuckles swells and turns black, blebs form, and half a dozen or more areas of superficial necrosis occur. The knuckles may be the only parts affected, or the extreme tips of the fingers. The patient may be incapacitated for a week or two, and a series of attacks may come on with changes in the weather. Winter after winter the trouble may recur, and, while never reaching a high grade, and only causing very superficial necrosis, the suffering and incapacity may be very great. In the cold, damp climate of the British Isles such cases are common. England is the land of chilblains, mild and severe, owing to the damp cold and to the insufficient heating, particularly of schools and institutions. Cold in itself is not the only factor, else these vasomotor disturbances would be more common in Canada, where, on the contrary, they are rare. If of transient duration, cold hands and cold feet have not the same import as the all-day-long lividity of these parts caused by working in rooms at a low temperature.

The "beefsteak" hand, a source of great annoyance, often of discomfort, is a permanent vasomotor disturbance, met with chiefly in young girls. While there are cases that persist throughout life, the condition may be transitory and associated with menstrual disorders. I have twice seen it with the slight hypertrophy of the thyroid gland of puberty. The color varies with the outside temperature—either cyanotic or hyperemic. The hands may be permanently swollen, and the cold, clammy feeling is very disagreeable. The hands alone may be affected, more often hands and feet, and there may be the "beefsteak" cheeks with permanent dilatation of the small veins, which are sometimes unpleasantly distinct. There are men of full habit, often of gouty stock, who have this same permanent engorgement of the bloodvessels of the extremities and of the face in a degree that passes the limits of health. In the winter the cyanosis may be extreme, and when there is much exposure the hands become very stiff and there may be numbness and tingling. In these cases it is a question altogether of cyanosis or hyperemia, not of local syncope; the extremities are either blue or red, not white, and they do not come into the category of the *formes frustes;* but there is a mild type of the disease, in which all these vascular disturbances recur in remarkable sequence. In middle-aged women, in connection with the paresthesia and numbness of the hands and feet—the acroparesthesia—there may be vascular changes, sometimes dead fingers—syncope most often, and slight grades of cyanosis.

(*b*) **Moderate Severity.**—A woman, aged twenty-five or thirty years, after perhaps a period of worry and ill health, begins to feel pain in the fingers or in only one or two fingers of each hand. Or it may be only a numbness and tingling, not actual pain, and the fingers feel stiff. Then

she notices that they have changed in color, are white and cold, and remain so for an hour or two at a time, gradually getting red and warm. Within a day or two a change occurs—they remain permanently blue, asphyxiated, perhaps to the second joint. The pain becomes more severe, and may require morphine. The tip of one finger or the terminal joint of another gets darker, and perhaps a few small blebs form. The other fingers show signs of restored circulation, but necrosis has occurred in the pad of one and in the terminal inch of another. The eschar of the pad of the finger gradually separates and healing takes place, with much less loss of tissue than had been anticipated. The necrotic phalanx shows a line of demarcation, and after a couple of weeks the bone is snipped off, but it takes a couple of months before healing is complete. The general health improves and the patient gets quite well. She may never have another attack, or, what is more common, in six months or a year there is a second. In many of these cases of moderate severity after two, three, or even four slight attacks complete recovery takes place.

(*b*) **Severe Forms.**—No more terrible malady exists than the severe type of Raynaud's disease. A man, aged twenty-five or twenty-six years, of a neuropathic disposition, begins to have numbness and tingling in the hands and feet, with local syncope. The feet become painful, and one morning he notices that they are livid to the ankles, slightly swollen, and so tender that he cannot put them on the ground. At the time the ears become swollen and red, with the margins very blue. The tip of the nose changes in color; within a few days the cyanosis has deepened, the toes are black, the feet purple, and about the ankle is a zone of a bluish-red color; it looks as if both feet would become gangrenous. A black line has formed at the margins of the ears and there is a small black spot at the very tip of the nose. The pain in the feet is atrocious. Pulsation is felt in the arteries. About the end of ten days the feet begin to look better, the circulation is reëstablished as far as the bases of the toes, which remain black, and a line of demarcation begins to form. Instead of losing both feet, only two or three toes of each foot may be lost, and a small rim of the ear and superficial abrasion of the tip of the nose. Within three or four months the patient is well. The greatest difficulty has been in the separation of the necrotic parts. The following winter the patient notices that the urine is bloody; the fingers begin to feel stiff and painful, and in a few days an attack is in full swing; this time he loses a finger or two. Three months later, before the hands have quite recovered, the right foot gets cyanotic and painful, the lividity extends above the ankle, and the gangrene is so extensive that the leg has to be amputated. For a year there may be good health, and suddenly the other foot becomes affected, the gangrene extends, and this leg, too, is lost. After a six months' respite the unfortunate victim may have an attack of such severity in the hand that the arm has to be amputated. In a few cases serious internal complications occur. The hemoglobinuria persists and the patient may die of it, or there may be attacks of severe abdominal colic. Cerebral symptoms may recur with each attack in the extremities, epilepsy, aphasia, transient hemiplegia, and the patient may die in coma.

The Symptoms in Detail.—The local *syncope*, the first stage, is the most characteristic single symptom; the others, cyanosis, active hyperemia, and gangrene, we see in many conditions; but except in Raynaud's disease the *dead white anemia* of a finger, of a toe, of one ear, is a rare phenomenon. Occasionally, in arteriosclerosis one sees spasm of the peripheral arteries and pallor of hand or foot, but such a persistent ischemia as that seen in typical cases is not met with in other pathological states. The fingers are most often affected, then the toes, the ears, and the tip of the nose. The whole foot or hand is not often involved. The anemia may be induced in a few minutes, giving a dead-white appearance to the skin. At first it may be patchy and gradually extends. Areas of slight discoloration may be seen before the ischemia is complete. Once fully established the finger looks "dead," and is cold and sometimes clammy like the finger of a corpse. The temperature may be 20° to 30° below that of the adjoining finger or of the palm of the hand, and the part feels cold. The patient may complain of numbness or a heavy, painful feeling, sometimes of pins and needles. At this stage the pain is rarely extreme. The motility is impaired, and on attempting to move it the finger feels stiff. The duration of the ischemia is very variable—from a few minutes to an hour or more—very much less than the cyanosis or active hyperemia. The attacks may recur eight or ten times in a day. Mild grades of local syncope are often seen in the "dead fingers" of nervous and neurasthenic individuals, but the ischemia is not complete, the color is not often of a dead white, and it is not associated with the reactions of the attack of Raynaud's disease. The paresthesia

Fig. 69

Raynaud's disease, showing superficial gangrene.

Fig. 70

Raynaud's disease, showing superficial gangrene.

may be marked, particularly in the cases of "waking" numbness. Occasionally in healthy persons local spasm of the arteries causes a patchy ischemia of the skin. It is sometimes seen under emotional excitement.

A good imitation of this condition may be had by making artificial anemia of one finger with a rubber ring. Within a minute the temperature drops and there may be numbness and tingling. The sensation is not nearly so unpleasant as if the light ligature is placed around the finger while full of blood. A useful demonstration is to produce the local

FIG. 71

Raynaud's disease, showing superficial gangrene of one toe.

syncope with a rubber ring rolled up the index finger from the tip; tie a ligature tightly about the middle finger, and in a minute cyanosis will be present; then if the circulation is reasonably active there will be the pink skin of the ring finger in active hyperemia, the cyanosis of the middle, and the ischemia of the index finger. The local syncope may disappear in one of two ways—the taps may be turned suddenly and the vascular areas are immediately flushed with blood, just as happens when the ring of rubber is removed, the anemia of the finger is instanta-

neously obliterated, but much more frequently it is a slow process, and a mottling appears and gradually the *second stage* of the process is produced.

Local Cyanosis or Asphyxia.—This has been called by various names—local apnœa, acrocyanosis, acro-asphyxia—but the first names are the most appropriate. This may come on without a previous stage of syncope; at any rate, syncope is not always seen. The color is variable, from a reddish blue to a blue black, sometimes an ashen gray, and if it persists for a long time, an intense indigo blue. The finger nails may be of an inky black color. There may be shades and mottlings of color from a light grayish blue to an intense blue black and an inky black. Pressure with the finger causes an area of anemia which is very slowly obliterated. With the cyanosis the finger is swollen but not œdematous. The temperature is lowered—8° or 10°. Riva measured the temperature before the attack between the thumb and index finger at 35.8° C.; in the attack it was 20.6°, and that of the hollow of the hand 23.4°. Even in a warm bath the part may remain cold and cyanotic. The asphyxia may be intense in one finger while the adjacent one is in syncope. The color is due to the fact that the circulation is so slow that the capillaries are filled with red corpuscles, the hemoglobin of which is deoxidized. Normally in the capillaries of the skin the circulation is so active that the corpuscles have not time to discharge their full load of oxygen, but when from any cause there is stasis the corpuscles unload all they possibly can and the change in color is noticed immediately. Two events may follow the local asphyxia—active hyperemia or necrosis.

Active hyperemia is an important stage in Raynaud's disease. It may follow directly upon the syncope, more often it follows the asphyxia. After persisting for several hours, or even for a day or more, the color begins to change, the patient feels a throbbing, and gradually the circulation is restored and the cyanosis is replaced by a bright pink. The finger gets hot and throbs, the pulse is to be felt in it; the radial is full and large, if the hand has been affected, and a capillary pulse may be seen in the nails. This stage lasts a variable period, usually bearing some proportion to the duration of the cyanosis. While the sequence of white, blue, and red is the rule, there are exceptions; the process may begin in one finger with a transient hyperemia, and then the syncope follows and the cyanosis; a sequence of red, white, and blue. Monro gives the case of a physician who had had various vasomotor phenomena and whose hands in the morning, after he had washed them, were very red, then they became white and afterward blue. When the hand and fingers are involved, all three processes may be observed together—the hand may be of a deep red, one finger white and the others cyanotic, or adjacent fingers may be red, white, and blue. Persons subject to attacks, particularly of the milder forms, may bring on an attack of local asphyxia by going out in the cold, when the hands become blue, sometimes at once, sometimes with a stage of preliminary syncope; then when in the warmth the active hyperemia is quickly established and the hands get hot, throb, and are painful. If the asphyxia persists and the circulation is not reëstablished, there is danger of the final stage—

necrosis or *gangrene.* This may follow the local syncope or more commonly the asphyxia. The fingers or toes or the whole foot remain cold and dead without any attempt at recovery of the circulation; the color grows darker and one or two of the fingers, or the tip of one, in mild cases, becomes black. Small blebs with serum form and break, leaving excoriations, or the bullæ break and leave a dry, black skin. The extent of the grangrene is generally much less than the appearance of the part would indicate; a foot which looks hopeless at the end of the first week may by the tenth day show great improvement and the toes alone be gangrenous. The necrotic part is gradually marked off by a definite line, and the skin of the proximal part is inflamed, often with a dull, cyanotic appearance. The process of separation of the parts is very tedious and accompanied by great pain. It may take weeks for a big toe to slough off and months for the anterior part of a foot. When the sloughing reaches the bony parts it is well to help the process by surgery. In the ears the necrosis is usually very superficial, forming a black eschar along the edge of the helix. In successive attacks a considerable portion of the margins of the ears may be lost. It is rare to see much necrosis of the nose, and even when the asphyxia is very pronounced and gangrene looks threatening, recovery may take place with a very superficial loss of substance.

Symmetrical parts are usually but not always involved. The process may begin in both hands or both feet and extend to gangrene in only one foot or one hand. When the ears are involved superficial necrosis occurs, as a rule, in both. A typical attack may occur in only one extremity. Of the distribution of the gangrene Monro gives the following figures: In 43 per cent. of the cases one or both of the upper extremities was attacked; in 24 per cent., the lower extremities, and in 22 per cent., upper and lower limbs. Parts other than the extremities may be involved; in severe attacks in which the ears are affected the cheeks may be dusky red and swollen and threatened with gangrene. The chin may be the seat of local syncope or asphyxia. In rare instances the tongue is attacked. In Powell's case the tip became deeply cyanotic, and a superficial ulcer formed. The lips have been the seat of both syncope and asphyxia; the nates and the labia majora have been attacked. Raynaud describes a case of local and painful asphyxia of the nipples. The eyelids have been involved. The cases in which local gangrene occurs on the trunk and the proximal parts of the extremities are rarely Raynaud's disease, but postfebrile gangrene and other forms.

Other Local Changes.—With recurring attacks of local asphyxia the hands may get thick and coarse. Rolleston describes a case in which they became visibly larger. Marked thickening of the skin of the fingers and a parchment-like induration may occur suggestive of scleroderma. In a few cases this disease has directly followed repeated attacks of local asphyxia. A well-marked instance of this kind is reported under the section on Scleroderma. The nails may be much altered in color, of a dark brown or brownish black, rough, ribbed longitudinally, and where partial necrosis of the phalanx has occurred they are greatly deformed. Suppuration may take place at the root and prove very obstinate. Des-

quamation of the skin of the fingers occurs if the cyanosis has lasted for a day or two.

Disturbances of Sensation.—Pain is an element of the first importance in all severe forms, particularly when the stage of gangrene is reached. The patient dreads to have the parts touched, or the slightest contact of the clothes causes agony. It is not confined to the affected parts, but may pass up the legs or arms, and may reach an intensity that causes the patient to cry out. Extreme local cyanosis may occur without much actual pain, and one rarely sees the pain of erythromelalgia unless necrosis has taken place. The worst attacks I have seen were in hysterical subjects and in very neuropathic Hebrews. In the severe attacks of local asphyxia the fingers may throb and ache as in chilblains. The local syncope may be painless, but in instances preceding gangrene the pains may be the first symptom and even antedate the ischemia. Occasionally the whole course of the disease is painless. One of my patients lost the tip of one index finger without any pain, but in other attacks during the three years in which he was under observation the pain was often atrocious. In another case the index finger was not painful, only numb, but the adjacent middle finger, in very much the same condition and with one gangrenous bleb, was very painful; and after he recovered, although the pads of the two fingers looked very much the same, glossy and bluish white, that of the index finger felt only a little numb when touched, but the skin of the middle finger was exquisitely tender.

Anesthesia, a dull numb feeling, is usual with the local syncope; paresthesia, tingling, and prickling are present during the asphyxia, sometimes an unpleasant throbbing and burning. Following the attacks there may be extreme hyperesthesia of the affected fingers or toes, and for months the patient may not be able, for example, to use the hand, on account of the sensitiveness of the finger tips. Cases with dissociation of sensation are usually syringomyelia.

Sweating may be present in the stage of local syncope; the finger may be covered with a cold sweat. In the active hyperemic reaction the whole hand may be moist, and in the protracted asphyxia a clammy moisture may cover the skin.

Motor Disturbances.—With the fingers dead and cold, motion is impaired, and they feel stiff, but, as a rule, there is not much motor disability apart from that caused by the pain. In a few cases wasting has been described in the interossei and in the thenars and hypothenars.

Complications.—If the symptoms of Raynaud's disease are due to an angiospasm of the peripheral vessels, evidence of similar changes should occur elsewhere in the body, and in two regions at least, the eye and the brain, such is the case.

Eye.—Raynaud himself noticed that there were coincident alterations in the retinal arteries. In a man with typical attacks of local asphyxia, during the period of reaction, the central artery of the retina and its branches had very clear contours, and were definitely narrower around the papilla than at the periphery, and here and there was a sort of partial constriction; the veins were dilated, elongated, and pulsated. In another case Panas observed a definite relation between the state of the arteries

of the fundus and the cyanotic attacks, contracted when the fingers were cyanosed, widened when they returned to their natural color. These are exceptional events; as a rule, there are no changes in the retinal vessels corresponding in any way with those in the peripheral arteries.

I have looked in vain for signs of constriction in several very typical cases, in one when the local syncope of the hands was extreme. In the two cases with marked cerebral symptoms there were no visible alterations in the retinal vessels. In a remarkable case reported by Weiss, with symmetrical gangrene of the fingers and reddening with superficial gangrene of the skin of the left side of the face in the zygomatic region, there was retraction of the eyeball in the same side, narrowing of the palpebral fissure, and slight ptosis; phenomena which Weiss referred to the cervical sympathetic.

Brain.—Goodhart points out that many of these subjects of acrocyanosis have all sorts of feelings in the head, giddiness, dreaminess, depression, fainting, etc., which he thinks may be due to peripheral stasis in the cerebral vessels for which he suggests the name "bluebrain." We have learned to recognize angiospasm as an important factor in cerebrospinal lesions. Sclerotic arteries are particularly prone to spasm, and the multiform clinical picture in certain cases of arteriosclerosis can only be explained by a transient contraction of the bloodvessels, causing an ischemia and loss of function. The temporary amblyopia has been seen to be due to spasm of the retinal vessels, and the transient monoplegias, hemiplegias, aphasias, and even paraplegias, from which rapid and complete recovery takes place, cannot possibly be due to organic lesions, and are most likely the result of angiospasm in definite vascular territories. Identical symptoms occur in Raynaud's disease. Raynaud himself reports a case in a woman, aged sixty-two years, but the transient hemiplegia occurred two years before the symmetrical gangrene. Weiss reports transient aphasia, and Simpson temporary hemiplegia, both in patients having well-marked features of Raynaud's disease. It seems only reasonable to regard these attacks as due to vascular changes in the brain of the same character as those which occur in the peripheral vessels. True, the arteries of the brain itself have not been found in spasm, but the ephemeral character of the attacks can scarcely be explained in any other way, and we have the visible demonstration in the eye of the transient loss of function in connection with spasm of the arteries of the retina.

Epilepsy.—Convulsions have occurred; in some the epileptic seizures have been independent of the local cyanosis, in others the association has been very close. The case reported from my clinic by H. M. Thomas,[1] one of the most extraordinary in this respect, illustrates the wide symptomatology of the disease. A man, aged twenty-three years, had typical Raynaud's disease—fingers, toes, ears, nose—and the cyanosis often proceeded to superficial necrosis. The attacks only occurred in the winter; in the warm weather he was perfectly well. Epileptic attacks accompanied the outbreaks of local cyanosis, but only in the winter,

[1] *Johns Hopkins Hospital Reports*, 1891, ii, 114.

when he had hemoglobinuria also. We followed his case with great interest for more than three years. The local cyanosis was very marked, but the necrosis was never widespread. He lost a little of the ear margins, of the tip of the nose, and of the pads of the fingers. After three years the epilepsy ceased, but the winter attacks of cyanosis came on as usual and were associated with crises of abdominal pain, just like those of angioneurotic œdema, and he had swelling of the spleen.

Mental Troubles.—The subjects are very often neurasthenic and subject to great depression. In hysterical patients, during the attacks the mental symptoms may be aggravated. There are no psychical disturbances peculiar to the disease. In a large number of mental disorders attacks of Raynaud's disease have been described—mania, amentia, melancholia, circular insanity, and progressive paralysis of the insane.

Organic Lesions of Brain and Cord.—Except the complications referred to above, there are no features of Raynaud's disease suggestive of coarse lesions of the central nervous system. On the other hand, local cyanosis and trophic disturbance are exceedingly common in many organic diseases of the brain and cord. These have often been described as cases of Raynaud's disease, but they are the vascular and trophic lesions well recognized as occurring in myelitis, syringomyelia, and tumor of the cord.

Urinary Changes.—*Hemoglobinuria.*—Albuminuria may occur during the attacks in paroxysmal form, or it may be permanent. Actual nephritis is rarely present. Hemoglobinuria is the most remarkable complication and occurs in a considerable number of cases. The well-known surgeon Druitt described his own case.[1] The attacks were brought on by worry or exposure to cold, and were associated with local cyanosis, numbness, and tingling of the extremites, and at times these features were suggestive of imminent gangrene. In Raynaud's disease only 37.4 per cent. of the cases are in males, but in the cases of hemoglobinuria with Raynaud's disease the proportion is 71.4 per cent. of males. As a rule, the urinary changes are only met with during the existence of the local cyanosis, and the attacks are more liable to occur when the patient is up and about. When put to bed the hemoglobinuria may cease, although the paroxysms of local cyanosis recur. The influence of cold is the most remarkable feature; a patient may be free during the warm weather, as in one of the cases mentioned above, but with the onset of cold weather the attacks begin and may recur at intervals through the winter. As Barlow pointed out, this is exactly what happens in the cases of ordinary paroxysmal hemoglobinuria. During the attacks the spleen may be enlarged. Abdominal colic occurred in my case. So far as I know, jaundice has not been described in these cases. Various changes in the blood have been described—hemoglobinemia with irregularity of the corpuscles and disinclination to form rouleaux. The connection with the vasomotor phenomena remains obscure. Possibly in the cyanosed areas changes occur in the serum of the stagnated blood which give to it a hemolytic quality, but we have in reality no reasonable explanation of the remarkable phenomenon.

[1] *Medical Times and Gazette*, 1873.

Skin.—In a few cases purpura has occurred. Urticaria has been present and has recurred with the paroxysms. The relation between true Raynaud's disease and scleroderma has been much discussed. Repeated attacks may give a hard sclerosed aspect to the fingers. It is certainly rare for generalized scleroderma to follow the recurring attacks of Raynaud's disease; there are a few cases, however, with this sequence. Barlow mentions a case with typical local syncope of the finger tips which ended in symmetrical gangrene of the tip of each index finger. She recovered, but the fingers presented an atrophied and contracted appearance; subsequently, extensive scleroderma of the skin of the chest walls came on and she died marasmic. Much more commonly, as the scleroderma develops on the hands and feet there is local cyanosis and trophic changes in the finger tips and in the knuckles. Local necrosis occurs, and the terminal phalanges become shrunken and contracted.

Heart and Arteries.—In a few cases organic heart lesions have been present. The extraordinary acrocyanosis of congenital heart disease never goes on to necrosis. Occasionally in mitral and tricuspid lesions in children the cyanosis of the fingers and toes may be remarkable. Embolic gangrene has in some cases of organic heart disease been mistaken for Raynaud's disease; in others there appears to have been a combination of the two conditions, as in Colson's patient (quoted by Cassirer), a four-year-old child with an organic valve lesion.

Arteriosclerosis is not a common feature, but it may be present. In long-standing cases definite changes in the arteries may be found. A patient of Barlow's had typical attacks of local syncope and cyanosis, and in his second winter a little gangrene of the second and third toes of the left foot. Two years afterward the toes of both feet became very blue and gangrene involved the left foot and ankle. Amputation of the thigh was done. The arteries were found to be diseased. The right toes showed signs occasionally of local asphyxia, and two years later the foot became gangrenous and necessitated amputation of the right leg. The arteries were found diseased. Barlow remarks that this case approximated to one of Friedländer's obliterative arteritis, and it seems reasonable to suppose that the recurring spasmodic contractions of the vessels brought about a permanent alteration in the walls and lumen. In the very large group of cases of local gangrene due to arteritis it is by no means easy to say whether the condition is Raynaud's disease or not.

Joints.—In recurring attacks in the fingers the terminal joints may be ankylosed by periarticular thickening, and in long-standing cases the last phalanges may be bent at right angles. Effusion may take place into the larger joints (knees), as in a case reported by Southey. The most remarkable case is one reported by Weiss: "There was effusion in the joint cavities and infiltration of connective tissues above and below the joints; once there was synovitis of the metacarpophalangeal joint of the right middle finger followed by tenosynovitis of the flexor tendons of the finger." The occurrence of Raynaud's disease with arthritis deformans is discussed elsewhere in this system (McCrae).

Diagnosis.—Let me define again the main points: Raynaud's disease is an affection of the vasomotor (and trophic) centres, the anatomical

basis of which has not yet been determined. The symptoms are associated with pain and vascular disturbances of the extremities—fingers, toes, hands, feet, ears, nose—local syncope, hyperemia, asphyxia, local necrosis, usually occurring symmetrically and in recurring attacks. Sensation and motion are not involved, but in some cases there are symptoms indicative of involvement of the vascular territories of the brain (aphasia, hemiplegia), kidneys (hemoglobinuria), and intestines (colic). The disease is most common in neuropathic individuals and women are much more frequently attacked than men. Few affections have more striking characteristics, and yet the difficulties in diagnosis are often very great.

Mild Forms.—If we could make necrosis the criterion and call no case Raynaud's disease unless the vascular changes had proceeded to gangrene, the diagnosis would be simple enough, but we cannot possibly exclude the milder forms, which escape this final stage. For years a patient may have recurring attacks of local syncope and asphyxia, with pain and great disability, but each time the cyanosis yields or disappears in an active hyperemia. Then in an attack, it may be the tenth or twentieth, the cyanosis of one finger does not yield, necrosis occurs, and the tip of a finger or an entire phalanx is lost. Or, what is still more common, the local asphyxia persists long enough to cause a slight superficial necrosis of the pads of the fingers or of the tips of the knuckles, a bleb forms, and there is left a superficial scar. Many cases go no farther—typical cases, which never reach the stage of severe gangrene. But here arises the difficulty—where are we to draw the line in these mild forms? It is not possible—Nature draws no hard and fast lines. Thus, there are cases of chilblains with every feature of Raynaud's disease; indeed, we may say that this remarkable affection represents the typical *forme fruste* of the disease; but we very properly hesitate to group all forms of chilblains under Raynaud's disease, and yet some of the most typical and serious cases of Raynaud's disease have been preceded by ordinary chilblains, and the attacks have never come on except in the winter months, after exposure. It is the sequence of events and the periodicity that characterize the disease, not the individual elements.

Two affections with many points of similarity, erythromelalgia and scleroderma, will be considered separately. Of many forms of local necrosis which have to be distinguished, the more important may be grouped under four headings—organic disease of the nervous system, obliterative arteritis, postfebrile necrosis, and multiple neurotic skin gangrene.

Diseases of the Nervous System.—*Syringomyelia.*—In no other organic affection of the nervous system is the condition of the fingers and toes more similar to that in Raynaud's disease, and yet in the majority of cases the added disturbances of sensation and motion make the diagnosis easy. It is more particularly in the form with sclerodactylism (Morvan's disease) that the mimicry is seen. The following differential table, modified from that of Castellino and Cardi, quoted by Cassirer, gives the essential points:

Syringomyelia.	Raynaud's Disease.
1. Begins gradually.	1. Begins suddenly.
2. Course very chronic; ten to fifteen years.	2. Course more acute; one to three months.
3. Begins usually in one extremity and extends slowly to the others.	3. Symmetrical onset the rule.
4. No previous vasomotor changes.	4. Vasomotor changes marked.
5. Recurring painful panaris.	5. Dry gangrene.
6. Skin cyanotic and cold.	6. Skin black and cold.
7. Dissociation of sensation.	7. Anesthesia or paresthesia.
8. Atrophy of muscles.	8. Atrophy very rare.
9. Ulceration common.	9. Ulceration rare.
10. Nails lost, and when reformed much curved and thick.	10. Nails dark, not deformed.
11. Necrosis and separation of bone.	11. } Atrophy of terminal phalanges
12. Fingers much curved and contracted.	12. } only.

Diseases of the Brain.—In hemiplegia the hand and foot of the paralyzed side may show marked vasomotor changes, great congestion, œdema, and occasionally necrosis of the fingers or toes. I have already referred to the cerebral complications of the disease, the transitory aphasia and hemiplegia which may accompany or precede the other manifestations, and in some of the cases in which Raynaud's disease has been said to complicate hemiplegia the peripheral and central symptoms have been due to one and the same cause. The hemiplegia of Raynaud's disease is usually transitory, and occurs in the subjects of repeated attacks of local syncope or of symmetrical gangrene. In organic hemiplegia the trophic changes leading to gangrene have rarely the same distribution as the necrosis of Raynaud's disease; the heel or the inner part of the ankle or the sole of the foot is as likely to be attacked as the toes, and there is not the same sequence of vasomotor changes.

Diseases of the Spinal Cord.—In many affections of the cord, acute and chronic, the most marked trophic changes may occur, leading to gangrene, and while the picture may resemble somewhat that of Raynaud's disease, there is rarely any difficulty in diagnosis. With chronic affections, in tabes and in tumor, trophic lesions of the toes and of the skin of the feet may occur, with a striking similarity to the lesions of the disease under consideration. Much more common is the trophic change without any vasomotor phenomena. Asphyxia of the feet in tabes may precede the appearance of the perforating ulcer. Schlesinger has reported a case of sarcoma of the cord with symmetrical gangrene of the toes. In acute myelitis the trophic changes have rarely the features of Raynaud's disease; the toes may not be affected, but the heels, or multiple patches occur on the legs. The gangrene comes on with greater rapidity. Following trauma and in all varieties of acute compressive myelitis local gangrene may occur, but the "acute bedsore," as it is called, is a very different lesion in distribution and in appearance, and could never be confounded with Raynaud's disease.

Multiple Neuritis.—Remarkable vasomotor and trophic changes may occur in neuritis. One of the most common is the loss of control (paresis) in alcoholic neuritis, with an extraordinary cyanosis of the hands and feet. Still more remarkable changes may be seen in the acute neuritis

of the infectious fevers—the hands may be swollen and cyanotic, but I have never seen necrosis. In the neuritis of the arm which sometimes follows arthritis of the shoulder-joint I have seen the whole forearm and hand swollen, painful, and red, except the finger-tips, which looked livid, as though about to become necrotic. There are cases in which a multiple neuritis with motor paralysis and vasomotor changes has been associated with local gangrene. Cassirer, after a careful analysis of the literature, concludes that genuine instances are very rare. Occasionally with the polyneuritis of beriberi there is extensive gangrene.

In the obliterative arteritis group, pain, paresthesia, and disability may precede the gangrene and the picture may suggest a neuritis. Still more suggestive are some of the diabetes cases with anesthesia or paresthesia, and a sudden onset of the gangrene. On the whole, it is not difficult to separate the vasomotor and trophic changes of neuritis from those of Raynaud's disease.

Obliterative Arteritis.—The local gangrene of this condition has many points in common with that of Raynaud's disease, and the two are often confounded. The cases, which are by no means uncommon, are met with in elderly people, in young persons who have well-marked arteriosclerosis, in syphilitic subjects, and in diabetics. Preceding the gangrene there may be attacks of the most extreme vasomotor changes. They are very obstinate and distressing, and the pain may be very severe.

Many of the cases present the interesting combination of obliterative endarteritis, intermittent claudication, paresthesia, and pain, with necrosis of the toes or of the whole foot. There is not often difficulty in distinguishing them from Raynaud's disease, but in a few cases in young persons the arteriosclerosis may not at first be very evident and the picture may be very suggestive. There may be marked preliminary spasm of the arteries, so that the foot looks white, and attacks of local asphyxia may come at intervals of a month or six weeks before necrosis supervenes. Barlow gives a case of a man with typical Raynaud's disease with recurring attacks which necessitated the amputation of both legs at intervals of a couple of years; the arteries showed decided thickening of all their coats.

Diabetes.—The relation of *diabetes* to Raynaud's disease is of great interest, as cases of this disease have been reported with local syncope and asphyxia. In one of Raynaud's cases the first signs of local asphyxia preceded the diabetes eight years, and it is quite possible the two diseases may coexist. In a majority of the cases the symptoms are due to arteritis, and there is an absence of pulse in the dorsal arteries or the posterior tibials. The onset may be sudden.

Gangrene of the Acute Infections.—This form, which is very rarely confounded with Raynaud's disease, may be due to arterial or venous thrombosis, in which case it is usually confined to one limb; or it may be associated with a very profound infection or a cachectic state, when it is often multiple. Many of these cases have been described as Raynaud's disease, but the existence of the infection and the distribution of the gangrene are sufficient for the diagnosis. The embolic and thrombotic forms involve the limbs, usually the leg and foot or the whole hand,

Fig. 72

Symmetrical gangrene in malarial fever.

Fig. 73

Symmetrical gangrene in malarial fever.

rarely the fingers and toes alone. Pneumonia, typhus and typhoid fever, and septicemia are the most common infections with which gangrene is associated. In some epidemics of typhoid fever it has been a more common occurrence than in the ordinary forms, and when due to a peculiarly virulent infection there may be multiple areas. The same holds true of malaria, in which the gangrene may be very widespread, as shown in the accompanying figures from a case admitted to the Johns Hopkins Hospital.

Multiple Neurotic Skin Gangrene and Pathomimia.—This is one of the rarest forms and has been variously described as *acute multiple skin gangrene, neurotic excoriations, gangrénes disséminées et successives de la peau d'origine hystèrique*, and by Dieulafoy as pathomimia. Cassirer, whose account is admirable, could find only 13 cases (1901), 10 women and 3 men, but there are many more if we include the cases of simulation. Many of the patients have been hysterical, but not all. The question of simulation has always to be considered. I saw in Paris, in Dieulafoy's clinic, a man who had this type of gangrene, which became so severe in the left arm that a surgeon amputated it in August, 1906. The spots had appeared at intervals for nine months; some of them were 5 and 6 cm. in extent. In February, 1907, the spots began to appear in the right arm —areas of gangrene which took two or three weeks to slough off and left a deep scar. Many physicians were consulted, and the case attracted widespread notice. He came to the Hôtel-Dieu in April, 1908; the "disease" had lasted two and one-half years, and he had ninety-eight scars on the arms. A few days after admission eschars began to form on the left leg just above the malleoli. Nothing could be determined as to the cause—he had not had syphilis, he was not hysterical, there was no diabetes, and nothing to suggest a special trophic lesion. The rapidity with which the eschars formed suggested simulation—one would be in full progress in an hour or an hour and a half. He confessed to having made them with caustic potash, dominated by a fixed idea which so far possessed him that he consented to have the arm amputated. Professor Dieulafoy suggested the name *pathomimia* for this simulation of the effect of disease.[1] The cases are of interest in connection with Raynaud's disease, as a condition very similar may be produced. Anschutz has published five cases of gangrene of the big toe in military recruits, caused by carbolic acid; the toes had to be amputated. The view is gaining ground among neurologists that all of the so-called trophic hysterical lesions—the hysterical pemphigus, the hysterical ulcerations, and the hysterical gangrene—are simulated. In any case the form of multiple neurotic skin gangrene has little in common with Raynaud's disease, and any difficulty in the diagnosis should not often arise.

Ergotism.—In chronic poisoning with ergot a local gangrene may be caused which bears the closest possible resemblance to Raynaud's disease. The fingers and toes are chiefly affected and the gangrene is dry. Vasomotor changes with paresthesia and sometimes contractions of the muscles may precede it. The cause is the same, namely, spasm of the arteries;

[1] *Académie de Médecine*, June, 1908. Separate Brochure. *Histoire d'un Pathomime*

but ergotism is exceedingly rare, occurs only in certain countries, and usually in endemic areas. I do not know that a gangrene similar to Raynaud's disease has ever been caused by the medicinal use of the drug.

Treatment.—The general health of the patient should be carefully studied. Sometimes it is only with the removal of some source of worry that the disease is cured. Neurasthenic and hysterical conditions must be carefully treated. In the mild forms, more particularly, the general may be more important than the local measures. When influenced by cold and damp the patient should keep the hands and feet warm, and avoid, as far as possible, getting chilled. When attacks recur in the winter only, a residence in Florida or southern California should be recommended, or if residents of Great Britain they should arrange to winter in Egypt. One of my patients, after years of suffering, had great relief in southern California.

The milder forms which do not reach the grade of necrosis are best treated by massage, electricity, and hydrotherapy. Systematic friction of the fingers and hand, morning and evening for half an hour, helps to give tone to the bloodvessels. A dead-white finger may be made of a vivid pink color in a few minutes, or the cyanosis may be made to disappear quickly. There is no one measure more useful in these cases than massage if one can get it thoroughly carried out. It may be combined with hydrotherapy, such as the alternate hot and cold douche to the hands or wrapping them in wet cloths for an hour or two twice a day. A general course of hydrotherapy at an institute or at one of the spas may be helpful.

Electricity may be used, and was highly recommended by Raynaud, either as galvanism or the high-frequency currents. In the severe types it is of little or no service, but in cases of paroxysmal local asphyxia and syncope it is a useful adjunct to other measures. Barlow recommends the following procedure: "Immerse the extremity of the limb, which is the subject of local asphyxia, in a large basin containing salt and tepid water; one pole of a constant-current battery is placed in contact with the upper part of the limb above the level of the water, and the other pole in the basin, thus converting the salt and water into an electrode. As many elements as the patient can comfortably bear should be employed, and the current should be made and broken at frequent intervals, so as to get repeated moderate contraction of the limb. The patient should also be instructed to make voluntary movements of the digits while the galvanism is applied." In many cases a great and even insuperable difficulty in carrying out the local treatment is the pain, which is increased by the movements and by the electricity. Sometimes the radiant-heat baths are most satisfactory; in one instance the pain was greatly relieved, so that the patient could sleep, and the local cyanosis was replaced by an active hyperemia, which gradually subsided.

In the severe forms with necrosis in progress there are three indications: (1) To relieve the pain, for which local sedative applications may suffice, but very often morphine has to be given. The radiant heat may be tried. (2) To reëstablish the circulation in the asphyxiated area so as

to restrict the progress of the necrosis. Massage and other local measures are impracticable on account of the pain and the presence of the gangrene. Hot douches, immersing the limb in hot water, a hot-air bath, or the radiant heat may be tried. In a case of great obstinacy and recurring attacks of gangrene of the toes and fingers, Cushing suggested the use of Esmarch's bandage, so as to get the good effect of the active hyperemia following its application. A simple tourniquet may sometimes be used. The limb is bandaged lightly and made completely anemic; the tourniquet is then applied and kept on for a variable period. The process is usually so painful that in half a minute the patient is crying out, and the tourniquet has to be loosened. In other cases the anemia may be maintained for a minute or two. When the limb is free the blood surges into it and causes an intense hyperemia, which may invade the cyanosed areas of the foot or leg. Carefully practised, if the patient can stand it, this procedure gives the best results I have seen in these severe forms. It may be tried three or four times a day. The venous hyperemia alone, by Bier's method, may be employed, but one does not get the intense active hyperemia which follows Cushing's method. (3) Local treatment of the gangrenous part: The separation of the necrotic parts is a slow, tedious affair, and may take months. Antiseptic poultices, lotions, and aiding nature at times with a little surgery are as much as can be done. The parts adjacent are rarely fit for any more radical procedure. Putting the patient in a continuous warm bath for two or three weeks may be tried, particularly in cases with excessive pain. The heat also favors the separation of the slough.

Medicines are of very little service. One would suppose that amyl nitrite and nitrogylcerin would be helpful. I have seen in a paroxysm of local syncope and asphyxia the spasm gradually relax and the affected fingers grow red and hot after an inhalation of nitrite of amyl, but it is not always effective, and there are cases in which the spasm of the arterioles is not affected in the slightest degree by the drug. In the severe paroxysmal forms neither it nor the sodium nitrite appears to be of much service. For the pain opium in some form has to be used, at first locally with the other measures spoken of, and if insupportable it must be given by the mouth or hypodermically. There is great danger in the recurrent form in women of the morphine habit. I have seen three cases with this grievous complication, and it was impossible to say just how much suffering existed. In persons of middle or advanced age, with daily paroxysms of pain and cyanosis and threatened gangrene, Monro recommends opium, in pill form, in moderate doses. Antipyrin, phenacetin, and other analgesics may be tried. Ergotin has been recommended, but in cases with threatened gangrene I should say its use was contraindicated; on the other hand, there is no more useful drug in the mild types of vasomotor ataxia in young girls—the dead hands, with puffiness, and cyanosis or redness depending on the external temperature.

CHAPTER XXVII.

ANGIONEUROTIC ŒDEMA: QUINCKE'S DISEASE.

By Sir WILLIAM OSLER, Bart., M.D., F.R.S.

Definition.—Localized swellings of the skin and subcutaneous tissues of the face and limbs, appearing spontaneously, and lasting from a few hours to a day or two. The mucous membranes of the lips, pharynx, larynx, gastro-intestinal canal, and genitals may be simultaneously involved, or they may be affected alone. The lesions in the skin are usually painless, but may be associated with itching and a sense of tension. Recurrences are the rule, and the swellings may appear at intervals throughout life. The affection may occur in many generations, and in many members of a family. In the majority of cases it is not serious, but the gastro-intestinal form causes severe colic, and in a few instances death has been caused by œdema of the glottis. The affection is closely related to urticaria.

General attention was not called to the disease until the description by Quincke in 1882,[1] since which date there have been scores of communications on the subject. The literature is fully given in the *Index Catalogue of the Surgeon-General's Library*, 2d series, vol. xii, and in Cassirer's monograph.[2]

Nomenclature.—The name here adopted is the one in general use by English and American writers. Others are: Giant urticaria (Milton); urticaria œdematosa, urticaria tuberosa, wandering œdema; intermittent œdema, acute recurrent œdema; œdème rheumatismal essential; œdème rheumatismal à répétitions; and hydrops hypostrophos (Schlesinger). The nodosités cutanées éphémerès of Févérol, as I read his description, belong to the rheumatic subcutaneous nodules.

Etiology.—The disease is not uncommon. The writer has notes of 18 cases in private practice. There were 16 cases at the Johns Hopkins Hospital in a period of nearly twenty years among 23,000 medical cases. It is more frequent among the better classes. In my series women were much more frequently attacked—14 to 4. In the cases collected from the literature by Cassirer there were 70 men and 63 women. A majority of the cases are in persons under twenty years of age, but it may occur at any period. J. P. Crozer Griffith reports cases at one and one-half months, and the grandfather of one of my patients who had suffered from boyhood had occasional attacks after his ninetieth year. With advancing age the tendency to attacks lessens. In one man the attacks began after his fortieth year.

[1] *Monatsheft. f. prakt. Dermatologie*, 1882.
[2] *Die Vasomotorisch-trophischen Neurosen*, Berlin, 1912.

In a majority of the cases no exciting cause can be discovered. Unlike ordinary urticaria, digestive disturbances and errors in diet play a very small part. One of the writer's patients thought that the eating of fish was sometimes the cause of an attack. In one case strawberries and coffee would at once bring out the œdema, a peculiarity which had persisted for twenty-two years. On the other hand, some of the most obstinate cases are entirely uninfluenced by diet.

Nervous Influences.—This appears to be the most important factor. In the first patient I saw with the disease, a young dentist, who had recurring attacks in the eyelid and forehead, worry, overwork, or any depressing influence was liable to bring on the œdema. A nurse, subject to the malady, had at times to give up a patient, who caused her much anxiety, on account of the recurring attacks.

Infections.—Rheumatic pains, swelling of the joints, tonsillitis, and, in a few cases, definite rheumatic fever have accompanied the outbreaks. Giant urticaria may occur alone or with other skin manifestations. In children there may be fever, with constitutional disturbances, pains in the joints, severe colic, vomiting, and polymorphous skin rashes; in one attack, purpura; in a second, ordinary urticaria; in a third, angioneurotic œdema; in a fourth, colic alone. In my series of 28 cases, reported under the title (for want of a better) "The Visceral Lesions of the Erythema Group," there were several cases of this character.

Malaria has appeared to be a factor in a few cases (Matas). The intoxications have played no rôle in my series. Alcohol has been mentioned by a number of observers. Of the endogenous poisons the result of perverted metabolism—anywhere from the moment the morsel of food is rolled round the tongue until its constituents have been through the furnaces and are cast out as ashes and smoke—we talk a great deal but we know nothing, so far, at least, as this disease is concerned. In organic affections of the nervous system œdema is not uncommon, but the cases scarcely come in this category. In poliomyelitis anterior, in compression paraplegia, in peripheral neuritis, in monoplegias, œdema may occur, but the whole limb is, as a rule, involved, and it has not the transitory character of the form under consideration. In the neuritis of typhoid fever or of arsenical poisoning the œdema may be very localized. But in none of these conditions is the œdema exactly like the Quincke form—it is more permanent and often more extensive, and the same may be said of the posthemiplegic œdema. In rare cases œdema may occur in the region affected with the lightning pains of locomotor ataxia.

Emotional disturbances are very apt to bring on an attack, and some of the most obstinate cases are in neurasthenic subjects. At least one-half of the cases in my series belong to this type. One patient who described herself as "a bundle of nerves," and with "pain wherever I have a nerve," had had œdema for more than twenty years, scarcely ever passing a week without an outbreak. When I saw her the back of the left hand, the ulnar side of the right hand, and the skin over the left elbow were affected. The ears often became stiff, swollen, and red. She had had colic, and as a younger woman was subject to "bruises"—

blue spots which came out spontaneously. The irregular distribution of the swellings in these neurasthenic patients separates the condition clearly from the hysterical variety.

Many of the patients have had other nervous affections—migraine, neuralgia, and exophthalmic goitre. In the last-named disease, erythema, urticaria, spontaneous and factitious, are common, but very rarely giant urticaria; a persistent œdema of the legs may occur which may have the tense, indurated aspect of scleroderma. In the psychoses, angioneurotic œdema is occasionally met with. The patients are very apt to be depressed and a settled melancholy may ensue.

Menstrual disturbances may be associated with transitory œdema. As is well known, at each period there may be puffiness of the hands or of the face. In at least six of my cases the attacks were more likely to occur at this time, and in individuals strongly predisposed, or with the hereditary bias, the association is common. At the climacteric, vasomotor disturbances are frequent, and occasionally the waking numbness and the acroparesthesia are accompanied by swelling of the hands and feet and puffiness of the face.

In susceptible individuals a slight trauma may suffice to bring on an attack. Cold, which is an important factor in certain cases of ordinary urticaria, does not seem to play any part in angioneurotic œdema. In a few cases only the uncovered parts—face and hands—have been affected. In very sensitive subjects, placing the hands in cold water, a cold breeze on the face, or exposing the buttocks in a cold water-closet, have sufficed to bring on a local attack. In none of my patients did the season make any special difference.

Heredity.—This plays a very important rôle, and the cases in this category are of unusual severity. Quincke, Dinkelacker, Strubing, and others have reported families in which it has occurred. In the family I have described,[1] the table of which is given (hereditary angioneurotic œdema), the disease occurred through five generations and affected more than twenty people, causing at least two deaths. I have since seen incidentally two other members of this family, both with very severe forms of the disease. In the other member of this family, in the sixth generation, attacks of colic occurred for years before any local skin swellings made the diagnosis clear. Meanwhile, she had had her appendix removed, as the recurring abdominal attacks were believed to be due to appendicular colic. The severity of the hereditary form is illustrated by the cases of Griffith;[2] both father and daughter died of acute œdema of the larynx.

I do not think any of the families have been studied with sufficient care to get details as to the frequency of transmission through the mother or the father on the value of Mendel's law. In the family reported by me it was impossible to get accurate details, as the members had scattered far and wide, and one of them did not know of the existence of a peculiar disease in her family.

[1] *Amer. Jour. Med. Sc.*, 1888, xcv, 362.
[2] *British Medical Journal*, 1902, i, 1470.

GENEALOGICAL TABLE SHOWING ANGIONEUROTIC ŒDEMA IN THE FAMILY OF T.

I.	II.	III.	IV.	V.
Margaret,[1] b. 1762, d. 1834.	Samuel,	3 children, all affected; 1 died of it.	One girl affected.	
	Stacy.		*Hamilton*,	*Thomas*, *Lizzie*.
			Rebecca, died of it.	2 children, aged 17 and 11, one of whom has had an attack.
	Allan, 10 children, 3 affected.	*George*,	Almira, *Mary*, *Julia*, *Katie*, *Edward*, *Maggie*, *George*.	
		Emma, single.		
		Sallie, married; no children.		
	John M.	4 children; 1 affected.		

Hysteria.—Sydenham first recognized an œdema associated with hysteria. Charcot and his pupils made it the subject of several important studies. The common variety bears very little resemblance to the ordinary angioneurotic œdema, except that in both there is infiltration of the subcutaneous tissue. The affection is usually superimposed on some well-marked hysterical manifestation—a paralysis or a contracture. It is not paroxysmal or transitory, but persists often for as long as eighteen months or two years, and, as a rule, is accompanied by disturbances of sensation. The areas affected usually correspond with the natural divisions of the body, an arm, a leg, a mamma, *i. e.*, they are "geometrical" or "segmental," or conform to areas covered by articles of clothing, stocking, sock, or glove. The ordinary type of Quincke's œdema may occur in hysterical subjects, and many cases of the kind are reported; but the association is not so common as with neurasthenia. In not one of my cases did hysteria coexist. Edgeworth reported a series of cases[2] in which transitory œdema of a segmental distribution occurred in young subjects, and in three of the seven cases there were disturbances of sensation suggestive of hysteria. In one instance the duration of the attacks ranged from two days to thirteen weeks.

Pathology and Relation to Other Affections.—Is Quincke's œdema a disease *sui generis* or is it only a symptom-complex with relations more

[1] Those in italics have suffered with the disease.
[2] *Quarterly Journal of Medicine*, 1909, ii, 135.

or less close with other affections and a varied etiology? It is not easy to determine. An affection which "breeds true" through six generations and presents in each identical features seems worthy of special designation. But the œdema itself is only a symptom, behind which is the effective cause for which we have so far no clue. Œdema, like arthritis, is caused by a number of different agents, and as in many forms of arthritis we have to be content with anatomical and clinical features, so in this special variety of œdema it may be urged that even in the absence of a definite etiological factor the clinical features and the remarkable heredity suffice to raise it to the dignity of a disease. The chief difficulty arises when we consider its close relations. The special lesion is nothing but a wheal of urticaria "writ large." The difference is one of degree and amount of exudation, not of kind. The erythema of an ordinary wheal is often present, and while the plasma plus leukocytes forms the chief part of the effusion, red blood corpuscles do pass out of the vessels and a staining may be left. Milton's phrase, "giant urticaria," was most happily chosen. Ordinary urticaria has its visceral manifestations, and there are cases which Doctor A. will diagnose Quincke's œdema in this attack, and Doctor B. simple urticaria in the next outbreak, and both may be right.

Another interesting relationship is with purpura—which has an identical lesion—an exudate of blood, with a qualitative difference, the red blood corpuscles being in excess, and, as a rule, there is not serum enough to raise a wheal; but in every spot of purpura the three elements of the blood are poured out. Gastro-intestinal crises are common in certain forms of purpura, and as in angioneurotic œdema, they may antedate for months the cutaneous features, or may occur quite independently of them. It is additionally difficult to label Quincke's œdema as a special disease when we consider that in the same subject at different periods the skin lesions vary. In papers in the *American Journal of the Medical Sciences*[1] I have reported a series of cases, 28 in number, illustrating the visceral complications of a group of skin lesions characterized by erythema, purpura, urticaria, and œdema. In individual cases followed for a number of years, with the gastro-intestinal crises, various lesions occurred, so that in one attack the disease could be called Henoch's purpura, in another a multiform erythema, in a third simple purpura, in a fourth angioneurotic œdema. Certain cases of Quincke's œdema present this variability, and even in the hereditary form, the lesions may be those of a diffuse erythema, with exudation. The skin lesions are too unstable to be of value except for a most superficial classification, and the visceral manifestations are practically the same in the whole series. Indeed, there are cases of hemophilia which clinically come in this category. I have seen spontaneous ecchymoses, purpura, and intense colic so severe that appendicitis was suspected in a well-known "bleeder." In the absence of fuller knowledge we are really in a quandary, and have to be content with a clinical classification. An attempt to group them etiologically is very unsatisfactory, as we know so little about the true causes,

[1] 1895, cx, 629, and 1904, cxxvii, 1; *British Journal of Dermatology*, 1900, xii, 227; and Jacobi *Festschrift*, New York, 1900.

and there are few departments in which speculation is so easy and at the same time so useless.

There are four conditions in which exudative skin lesions (erythema, purpura, urticaria, œdema) are met with in connection with gastro-intestinal crises and sometimes more serious internal complications, as acute nephritis.

I. **Acute Infections.**—The clinical picture of Henoch's purpura or of Schönlein's disease or of an acute exudative erythema may be met with in rheumatic children, sometimes with arthritis, endocarditis or pericarditis, and there may be fever and the general features of an acute infection. The skin lesions may be associated with some other infection, as gonorrhœa, or with a local ulceration.

II. **External Poisons.**—A large group of substances, animal, vegetable, and mineral, possess the power of causing exudative skin lesions. All are sensitive and react to certain of these, but in a majority of cases it is not a general but a special condition of the recipient, a sensitiveness, an idiosyncrasy, as we say. Quinine will cause an erythema, iodide of potassium a purpura, strawberries an urticaria, shell-fish a local œdema, and the capability thus to react to certain substances may be inherited or "run" in a family.

III. **Endogenous Poisons.**—In diseases characterized by profound disturbances of metabolism exudative skin lesions are rare. In gout and diabetes the types of auto-intoxications, these complications are not often seen; they are more common in chronic nephritis. There is more evidence in favor of hepatic poisons—the oft-recurring urticaria in some cases of gallstones (even without icterus), and the frequency of purpuric and allied skin rashes in jaundice. The cases in children with recurring colic and gastro-intestinal disturbance associated with outbreaks of purpura or purpuric urticaria suggest an auto-intoxication, but we have no positive data, not a clue as to the nature of the poison or the locality of its formation.

IV. **Heredity.**—Certain persons are born with a special susceptibility to exudative skin lesions. There are families all the members of which present these reactions to particular substances; there are families some members of which are liable to attacks of local œdema, a peculiarity which has been traced through six generations; and lastly, there is an hereditary œdema of the legs (Milroy's disease) which has probably nothing to do with the forms under consideration. These are the main facts in connection with heredity and exudative affections of the skin and mucous membranes. There are all sorts of difficulties in the way of any satisfactory explanation of the remarkable phenomenon of localized œdema occurring in several generations. It is not like a chemical anomaly, as cystinuria or alcaptonuria—the susceptibility is only in certain individuals, and may be delayed until the forty-seventh year; it may occur early in life and then disappear, or it may last to an advanced old age. The inconstancy, the irregularity, is the most striking feature, both in distribution and in the incidence of attacks in affected families.

If we understood the pathology of an urticarial wheal we might discuss intelligently these remarkable varieties of local œdema. Gilchrist has

shown us how easily the anatomy of a wheal may be studied in factitious urticaria. Here a direct irritant, a scratch, is followed by a vasomotor hyperemic reaction, a perfectly normal phenomenon on a healthy skin; but in a sensitive person along the line of the irritation something else has happened; the capillary walls have been made permeable, and an exudate of all the elements of blood, but chiefly of the serum, forms the wheal. We have no idea why the same sort of scratch will in A cause hyperemia, in B anemia, and in C factitious urticaria. The vascular change is a vasomotor phenomenon—vasodilator or vasoconstrictor—but what is the change which permits of the exudate? Is it neurotic, an alteration under nervous influences of the rate at which the vascular cells secrete the fluid, or is it a physical change under the influence of the irritation, which permits a more rapid osmosis through the capillary membranes? If we could answer these questions for simple factitious urticaria we might approach the problems of the other exudative lesions in a hopeful mood. In the case of Quincke's œdema we have to suppose in certain areas a vulnerability of the capillary walls which permits of an exudate at so rapid a rate that the efferent channels cannot deal with it, and in consequence the lymph spaces are distended and the skin swells. Why this should occur in the lip today, in the gastric or intestinal mucosa next week, and on the hand next month—why it should come on in a perfectly healthy person and recur at intervals for a year or two and disappear completely, or why the liability should occur in families but only in certain members, and be transmitted for six generations—these are questions for which we have as yet no answer.

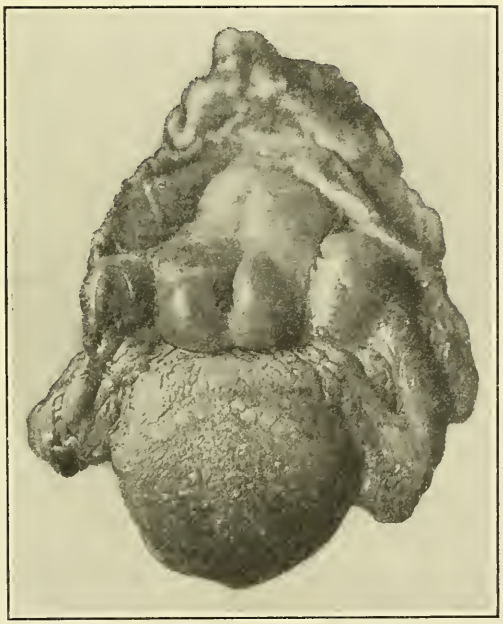
Symptoms.—There are three groups of cases, mild, moderate, and severe. A young woman who has been overworked or has had worries awakens one morning with a sense of itching over the forehead, and on looking in the glass is surprised to find one eyelid swollen and the side of the face and forehead puffy. By noon the swelling has gone. The lip may be œdematous, or there is a puffy swelling of the back of one hand, or a local infiltration the size of a saucer on the skin of one leg. The attacks recur at intervals for five or six months, or for a year or two, and then disappear. The œdema may always recur in the one place—the eyelid, a finger, or the back of one hand. The general health is not disturbed, and the outlook for complete recovery is good.

In a second group of cases the manifestations are more severe, and the disease lasts for a much longer period, even for a lifetime. The swellings are more voluminous, and troublesome by bulk alone. The hand may be like a boxing glove; the under lip may be so swollen that it is difficult to feed the patient; both eyes may be closed, the neck may be obliterated, both feet may be enormously swollen, or the penis may be so infiltrated as to impede micturition. In these forms the mucous membranes may be affected and the hemorrhagic œdema of the walls of the stomach may cause colic and vomiting, or in the intestines severe cramps or crises with diarrhœa. The mucous membrane of the mouth and throat may be involved, and in these cases the skin lesion is not always a simple œdema, but there may be erythema, with hemorrhages. The frequent recurrences of these manifestations may render the patient's life a burden.

The attacks may begin in childhood, and persist even to advanced old age, or they may not start until adult life, and then only persist for a few years.

In a third group of cases the localization of the œdema in the throat and larynx threatens life with each attack, and there are now in the literature half a dozen or more fatal cases. The case reported by Roger Morris[1] illustrates the serious character of some of these cases. A man, aged twenty-one years, had had repeated attacks of swelling of his feet and hands. Then he began to have the larynx affected, and twice tracheotomy had to be performed. In the fatal attack he was found sitting up in bed, with urgent dyspnœa, and before the doctor could reach the house he was dead. The illustration, Fig. 74, gives a picture of the extent of this form of sudden œdema of the glottis.

Fig 74



The larynx and neighboring tissues in angioneurotic œdema.

Character of the Skin Swelling.—As a rule, it is a simple œdema without erythema—an infiltration of the subcutaneous tissues and of the skin itself. The appearance depends on the degree of laxity of the tissues—the eyelid and the lip are the two types. In the former there is a gelatinous œdema, soft and puffy, which pits deeply, and which has a bluish-white tint. In the lip the swelling is firmer, may not pit at all, and has an opaque-white aspect. The skin is usually anemic and smooth; when

[1] *Am. Jour. Med. Sc.*, 1905, cxxx, 382.

the œdema is persistent, blebs may form. The appearance varies greatly with the stage—at the height of the exudation the areas are tense and opaque white, contrasting sharply with the surrounding skin; as the swelling subsides the skin becomes relaxed, and even flabby and wrinkled.

The size and extent of the swellings vary greatly and both hands may be as big as light-weight boxing gloves. There may be areas of infiltration as big as saucers or the size of a soup-plate on the trunk or thigh; the under lip and chin may be so swollen as to render the features unrecognizable and make eating and even breathing very difficult; or the outlines of the neck may be obliterated. In mild cases small areas, 2 to 5 cm. in extent, are present, or the back of the hand, one finger, or an eyelid swells, or there are half a dozen large wheals on the trunk. In all varieties the outlines are usually well defined, and in the case of the swelling of the hand there may be a ridge on the wrist an inch or more in height.

The color is not always opaque-white, but may be translucent or waxen, sometimes with a slight yellow tint. Erythema may be present even in large areas of œdema, as in the hereditary case already mentioned; and so marked may this be as to give an appearance of an acute inflammatory œdema. A transient efflorescence may be seen in an acute swelling of the lip or of the penis. In the smaller areas, which resemble rather large wheals of ordinary urticaria, there may be a zone of erythema. In regions where the skin is very loose, eyelids and prepuce for example, blebs may form.

The temperature is not raised; indeed, in the large areas with a deep œdema and much anemia it may be 6° or 10° below the skin of the corresponding part. In the form with erythema there may at first be an increase in the temperature, readily perceptible to the touch.

Subjective Sensations.—These may be absent altogether. One of my patients could not tell whether the forehead was swollen until she looked in the glass. She could tell immediately on waking whether the eyelids or the lower face were swollen by the stiffness and restraint in motion. Prickling sensations, a sense of burning, heat, and itching are common, but intense itching, such as is so distressing in ordinary urticaria, is very rare.

Regions Affected.—The face and extremities are the common situations. Among 71 cases, in 29 the first swelling was in the face, in 22 in the extremities (Collins). The irregular asymmetrical distribution is very characteristic of this type—an eyelid, one hand, the side of the thigh, the dorsum of a foot, the chin, one finger. In one of my patients, in whom the swelling was usually in the hand, as a rule both were affected, but sometimes only one. The segmental distribution is not common, but, as Edgeworth pointed out, it may occur in Quincke's œdema and be quite as marked a feature as in the chronic hysterical form. There are cases in which the swelling is always in the same place, usually the eyelid, a form to which ophthalmic surgeons have given special attention. A peri-articular variety has been described, and Rendu has reported the sudden onset of supraclavicular swellings resembling those of angio-neurotic œdema. The intermittent hydro-arthrosis and the intermittent

parotid swelling scarcely come in this category, although Schlesinger regards them as closely related affections.

Mucous Membranes.—One-half the cases in my series had involvement of the mucous membranes. By far the most common is swelling of the inner aspect of the lips and cheek, either alone or with the tongue. This may be in connection with a local œdema of the face, or in a person subject to attacks the mouth may be affected alone. The swelling may be diffuse or very localized. I have seen the very tip of the tongue involved. Very serious are the attacks in which the whole mouth, with the sublingual tissues and subcutaneous structures of the neck, is involved. The cavity of the mouth may be almost closed, and for some hours it may be impossible to take food or drink. The throat may be the seat of a local œdema confined to the uvula and the arches of the palate. The uvula may be as big as the thumb. The tonsils are rarely involved.

Respiratory Passages.—Much more serious is the œdema of the respiratory passages. The nose is not often affected. I have seen the external orifices nearly closed, and the mucosa involved with the skin. Isolated swellings of the turbinated bones or attacks like hay asthma are of rare occurrence. Bloodgood described a case which he called angioneurotic œdema of both accessory sinuses and of the cheeks. The condition persisted for months. The sinuses were opened and a condition of intense œdema of the mucous membrane was found.

Œdema of the larynx is a rare event. It does not often occur alone, but usually in association with swelling of the pharynx or with some external manifestation. The onset is sudden, very often in the night, and the patient wakens with dyspnœa and a feeling of heat and irritation in the throat. The condition may become rapidly worse and death may occur before help arrives. In Roger Morris' case, already referred to, the man's life had twice been saved by tracheotomy, and in the third attack the doctor arrived too late. In Griffith's cases father and daughter died of œdema of the larynx. One case, and possibly two, in the family I reported died with this complication. T. H. Halsted[1] has discussed fully these complications in the upper air passages. It has been suggested that certain forms of asthma belong to this disease, but I do not think this is very likely. None of my patients had asthmatic attacks, and I do not see any cases in the literature in which asthma alternated with well-marked skin lesions of the pure angioneurotic œdema type. On the other hand, the association of asthma with ordinary urticaria is well known, and I have seen one case in which, in repeated attacks, a crop of urticaria came out, with intolerable itching, over the spine in the region of the third and fourth dorsal vertebræ.

Conjunctiva.—This is rarely affected alone, but in the cases of œdema of the lids it is not uncommon to see the mucous membrane greatly swollen. Cases are reported with chemosis and little or no involvement of the skin.

The Gastro-intestinal Canal.—This is involved in about 34 per cent. of the cases (Collins); ten of my patients had attacks of colic. We know

[1] *Am. Jour. Med. Sc.*, 1905, cxxx, 863.

now the nature of the local trouble, as exploratory operations have confirmed the view that it was an œdema of the wall of the bowel, and in a case reported by Morris, in washing out the stomach to relieve the severe vomiting, a portion of the mucosa was removed, and on examination was found to be in a state of acute œdema.

Colic is the common abdominal symptom, coming on suddenly, and often reaching an extreme grade. As a rule, it occurs with the skin manifestations, but it may be the only feature, and there may be no clue to the nature of the trouble. In a majority of cases it is a "dry colic," the pain central, more or less continuous, with paroxysms of greater intensity. The patient may roll about in the bed or be doubled up in an agony of pain. The abdominal walls are tense, there is not often tympanites, and there may be no local tenderness. Appendicitis, gall-stone colic, or renal colic is suspected, and in a considerable number of cases laparotomy has been performed.[1] There are many instances in which the abdominal symptoms have preceded for months the onset of any skin lesions. In severer attacks with the colic there is vomiting coming on with the pain and lasting for many hours. The patient may look very ill, with pallor, small pulse, and features of collapse; and at the end of ten or twelve hours the symptoms may all disappear, and an outbreak of local œdema gives the diagnosis. The gastric crises may be the most troublesome feature and may recur after the attacks of œdema of the skin have ceased.

With the gastric symptoms and colic there may be intestinal symptoms, diarrhœa, meteorism, and even the passage of blood. In my experience these have not been so common in the cases of pure angioneurotic œdema as in the group of closely allied cases known as Henoch's purpura. The abdomen may be swollen and tender, and the picture—sudden onset, vomiting, pain, diarrhœa, pallor, with feeble pulse—may suggest perforation of a gastric or a duodenal ulcer. The passage of blood in children may suggest intussusception. In no case in my series of angioneurotic œdema was there melena.

Renal Symptoms.—These are not common. Albuminuria has been met with, and in a case of Oppenheim's the state of the urine suggested an acute nephritis. Paroxysmal hemoglobinuria occurred in a case of Joseph's. When the abdominal pain is lateral or starts toward the pubes, renal colic may be suspected.

Cerebral Symptoms.—Cerebral symptoms have been reported, particularly in connection with the family form—headache, somnolence, vertigo, and marked depression.

Fever rarely occurs, but after a severe gastric crisis there may be a slight elevation of temperature, and for a day or two the tongue is furred and there is loss of appetite. It is surprising with what rapidity recovery may take place, and within twenty-four hours after the most alarming symptoms a patient may ask for solid food and have a good appetite.

Diagnosis.—Quincke's œdema is easily recognized—it is localized, white, transitory, and recurrent. Only in the few cases, such as those

[1] Osler, *Am. Jour. Med. Sc.*, cxxvii, 751.

reported by Edgeworth, when it is segmental and in the legs, could any difficulty arise. Ordinary intelligence is required to distinguish the various œdemas of stasis and of cachexia. The hysterical form is more chronic and has the characters already given. Milroy's œdema is confined to the legs and is hereditary. In a large majority of cases the lesions are the same in different attacks, and there is a predilection for the same locality; but in children and in young adults the lesions are polymorphic, and the case may be a typical angioneurotic œdema today, but next week there is a severe attack of hives, or an outbreak of purpura, or a periarticular region is erythematous and infiltrated.

It is not always easy to distinguish from the swelling of a local thrombosis, particularly the recurring form in young persons which Briggs described from my clinic. In a young chlorotic girl with multiple cutaneous swellings on the skin of the trunk the diagnosis of angioneurotic œdema was suggested, but there were thrombi in the veins of the legs. Where the thrombus is deep and the swelling very localized, as in the calf of the leg, the difficulty may be very great. I saw such a case with Dr. Ruffin, of Washington, in an exceedingly neurotic young man. It is rarely a white œdema, and it is much more persistent than the ordinary giant urticaria.

In one case the preliminary œdema of scleroderma was mistaken for Quincke's disease, but it was permanent and the hardening and change in color of the skin were soon apparent.

As a rule, with the skin lesions well defined, there is no difficulty in recognizing the cases, but it is a very different matter when the gastro-intestinal symptoms are dominant. Appendicitis is naturally suspected. The pain, as a rule, is much more severe, and the patient writhes about in the bed in a manner very unusual in appendicitis; local tenderness is rarely met with in the right iliac fossa; there is no fever, and lastly the attack is over in a few hours, from three to six or eight. In severe cases there are vomiting and diarrhœa and sometimes blood is passed per rectum. There are cases in which these attacks recur with great frequency, once a week or once in ten days, and in the absence of any skin manifestations it may be very hard to reach a diagnosis. A number of patients have been operated upon, either for appendicitis or for intussusception. In one case stone in the kidney was suspected, as the colic was always in the flank. One patient was operated upon for gall-stones and afterward for appendicitis.

The most serious internal complication, œdema of the larynx, is easily recognized, as it rarely occurs alone, but commonly in association with swelling of the lips or face. Mild grades of obstruction usually occur before a serious attack, but, as in the case mentioned, there may be very little warning. The features of acute obstruction are only too evident, and tracheotomy or intubation may be necessary to save life.

Prognosis.—The attacks usually recur, but many patients, after having the disease for eighteen months to two years, get quite well. The duration in my series ranged from eighteen months to a life of exceptional duration. The younger the patient the better the prognosis. The family form seems peculiarly obstinate, and may persist to advanced age.

When diet has a marked influence on bringing on attacks the outlook is good. The disease is rarely dangerous to life, and that always through the œdema of the glottis.

Treatment.—The general condition must be carefully studied. Many of the patients are neurotic, and a suitable course of hydrotheraphy, massage, and electricity may be given. An outdoor life is an important element in the cure. In young persons the outlook is usually good, particularly in children in whom the œdema is associated with colic, etc. Several patients in my series have now been quite free from attacks for eight or ten years. The angioneurotic œdema of the face, particularly of the eyelids in young persons, is singularly obstinate, and may resist all forms of treatment.

Careful inquiry should be made as to the influence of diet, and, as a rule, some change should be made or certain articles cut off. Coffee or tea may be the offending substance, or the patient may be eating too much meat. One patient in whom the attacks were very frequent was benefited by a milk diet. In strong, full-blooded persons the use of laxatives may be helpful. I tried a salt-free diet with one patient without any success. On the whole, my experience has been against any special influence of diet in the disease. In children some of the very protracted forms seem to be associated with gastro-intestinal trouble, which should be carefully treated. Many cases have been dealt with on the view of intestinal intoxication. In a woman with great flatulency, irrigation of the large bowel was helpful. Many medicines have been recommended: strychnine, the bromides, alkalies, the salicylates, antipyrin, ergot, belladonna, etc.; and in the chronic cases it is only natural that all sorts of drugs should be tried. I have only found two of service: nitroglycerin or the nitrites, given in ascending doses until effects are felt, *i. e.*, until the patient feels the flushing and the headache. It is useless to order simply one or two minims of a freshly made 1 per cent. solution of nitroglycerin. The dose must be gauged to the individual, who should be told to increase it gradually until he feels the effects, and then let him continue the treatment for periods of ten days, with intervals of five days. The other drug is calcium, recommended by Wright. In this group of cases I have given it a thorough trial, and in two out of five cases it seemed most helpful. In Case 18, a young man who had had very severe attacks, and had been under treatment for eighteen months, was rapidly relieved, and although he had a few recurrences he has now been a year without any œdema. He took calcium lactate, 20 grains (gm. 1.3) three times a day. Various organic extracts, particularly the suprarenal, have been recommended.

In children with attacks of colic and periodic outbreaks, gray powder, given for a week or ten days at a time, has seemed helpful.

The gastric and intestinal crises require prompt treatment—a hypodermic of morphine gives immediate relief; but it is well to be careful in the hereditary and recurrent forms, and, if possible, use strong carminative and local applications. In a case with recurring attacks of œdema of the larynx, an intubation apparatus should be in the house, and some one should be taught its use in case of emergency.

HEREDITARY ŒDEMA OF THE LEGS (MILROY'S DISEASE).

In 1892 W. F. Milroy, of Omaha, reported, under the name of "An Undescribed Variety of Hereditary Œdema,"[1] a remarkable series of cases, characterized by persistent œdema of the legs. The disease affected 22 individuals among 97 persons in six generations. Dr. Milroy wrote to me about the cases, which I at once recognized as peculiar, and, so far as I could ascertain, undescribed. A note in the condition was made in my text-book under angioneurotic œdema. Meige,[2] in 1898, described eight cases in four generations, and a good many cases have been reported in France. In 1902 Rolleston[3] reported 3 cases in two generations, and in 1908 Hope and French[4] described a remarkable family in which 13 members were affected out of 42 persons, traced through five generations. The following are the important features:

Heredity.—The affection may persist through five generations. The percentage of persons affected varies from only 2 or 3 in certain families to nearly 20 per cent. among 97 persons in Milroy's family. Males and females are about equally affected, and we have no explanation of why one individual rather than another is attacked. As in other diseases chiefly familial, cases occur sporadically, and no doubt some of the forms of persistent brawny œdema of the legs, beginning in childhood or early adult life, belong in this category.

Absence of all Local and General Causes of Œdema.—There are no evidences of thrombosis in the veins, or of lymphatic obstruction, nor are any of the constitutional causes of œdema present, and the patients are usually in good health.

The Local Condition.—The legs alone are involved. The œdema may appear shortly after birth or the onset may be delayed until puberty or even until adult life. Once established it is permanent. The extent is variable; it usually stops at the knees, and may involve only the ankles. In long-standing cases the swelling reaches the thighs, and the feet and ankles become œdematous, as shown in the accompanying figures (Figs. 75 and 76). The swelling is painless, increases in the standing posture, and naturally tends to become very hard and brawny. The veins are not enlarged, and there is no redness. By careful bandaging the swelling may be kept under control, and a patient may do hard work until an advanced age.

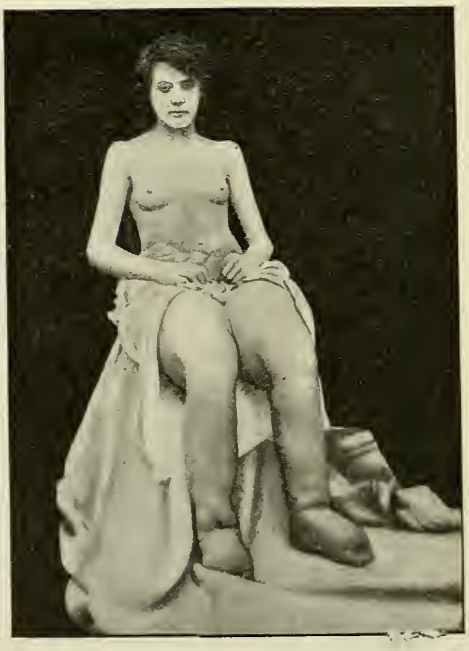
Acute Attacks.—In many cases, particularly noticed in the Hope-French series, there are remarkable attacks of fever (usually following the onset of the œdema), possibly angioneurotic crises such as occur in the ordinary angioneurotic œdema.

Diagnosis.—This is never in doubt, once the family character is established, and the absence is determined of all the ordinary causes of œdema—cardiac, pulmonary, renal, leukemic, or local in the pelvis,

[1] *New York Med. Jour.*, 1892, lvi.
[2] *Presse Médicale*, 1898.
[3] *Lancet*, 1902, ii.
[4] *Quarterly Journal of Medicine*, 1908, i.

Fig. 75

Fig. 76



Hereditary œdema of the legs (Milroy's disease). From the *Quarterly Journal of Medicine.*

veins, or lymphatics. A point to which several observers have called attention is the existence of other nervous troubles in members of the family, as epilepsy, insanity, or imbecility.

Treatment.—The acute attacks require opium for the pain, and, locally, soothing lotions to the legs. It is doubtful if anything can control the tendency to the œdema. By far the most successful measure is persistent bandaging, which keeps the swelling in check. This was well illustrated by several members of the family described by Hope and French, who had in this way kept the swelling under control and lived for more than sixty years. Unless bandaging is done, the œdema gradually extends, and when it reaches the extent shown in the figures it is impossible to do much for it.

CHAPTER XXVIII.

DIFFUSE SCLERODERMA. ERYTHROMELALGIA.

By Sir WILLIAM OSLER, Bart., M.D., F.R.S.

DIFFUSE SCLERODERMA.

Definition.—A nutritional disturbance of the skin, patchy or diffuse, leading to induration and atrophy. The pathology is unknown, but it is usually considered to be a trophoneurosis. A local and diffuse form is recognized; the latter only is here described.

Incidence.—The disease is more common in the United States than the published reports indicate. From May, 1891, to May, 1905, I had under my care 18 cases, and I saw incidentally 2 others. To May, 1905 (a period of sixteen years), there had been 18 cases of scleroderma in the medical wards of the Johns Hopkins Hospital. The cases are more numerous in the general medical and the departments for diseases of the nervous system than in the dermatological clinics. Crocker states that of 10,000 cases of skin diseases in out-patient practice, there were only 8 cases of scleroderma: 2 diffuse and 6 circumscribed. It is more common in some countries than in others, and is stated to be rare in Germany. Lewin and Heller in 19,000 patients and 1800 skin cases saw only one instance of scleroderma. At the Vienna Dermatological Society in 1902, Neumann made the remarkable statement that scleroderma had only been known in that city for eighteen to twenty years, and that Hebra "had never seen a single case." In Oppenheim's clinic, among 7000 cases of diseases of the nervous system there were 7 cases.

Etiology.—*Sex.*—Women are more frequently affected than men, 67 per cent. in the collected cases in the monograph of Lewin and Heller (1895).

Age.—A majority of the cases are between the ages of twenty and forty years. A considerable number of cases occur in children, in whom the disease is more apt to be acute.

Heredity.—In a few cases, members of the same family have been attacked. A woman, aged twenty-eight years, had a brother and a mother who had had the disease, and Cassirer gives four or five cases from the literature in which relatives were affected.

Acute Infections.—These are believed to play the most important rôle in the etiology. Cases have followed influenza, acute otitis media, diphtheria, pneumonia, typhoid fever, erysipelas, scarlet fever, tonsillitis, tuberculosis, and syphilis. In several of my cases the disease was supposed to begin with "rheumatism," but the joint troubles were really the initial symptoms. In one the severe arthritis antedated the scleroderma five or six years—the joints were swollen, hot, and red, and there were several attacks before the final one in the elbows and wrists, after

which the scleroderma began. The cases after the infections have often been more acute, and large areas of skin may be involved in a few days. In a few cases the disease has followed a septic puerperium.

Among favoring causes which have been mentioned are disturbances of menstruation, neuropathic disposition, protracted cold, emotional disturbances, trauma, psychical shock, migraine, alcoholism, etc. In looking over the histories of the eighteen cases in my series, it is not possible to say that there was any one etiological factor of special moment. That in two or three cases the symptoms followed an acute infection may have been quite accidental. In a majority the disease attacks healthy persons who had had only the ordinary wear and tear of life.

Pathology.—In only one case of the series, No. X, did I have an opportunity of having a postmortem examination. Dr. Flexner made the autopsy, and the histology was very thoroughly studied under his direction by Dr. Bates Block. The following is a summary: There were no evident changes in the brain or spinal cord. The hypophysis was normal. The thyroid gland was healthy. The adrenals showed central cavities, due to hemorrhage, but no finer alterations. The arteries showed extensive arteriosclerosis (he was a man of forty), with marked thickening of the walls of the small vessels, and atheromatous changes and areas of calcification in the aorta and femorals. The peripheral nerves showed thickening of the connective-tissue sheaths, but no alteration in the fibres themselves. The skin presented the changes which have been so often described—sclerosis of the arteries, particularly of the smaller ones, which showed endarteritis and in places obliteration. There was an increase in the elastic fibres below the papillary layer, extending into the subcutaneous tissues. The connective tissue was present in coarse homogeneous bands, running parallel to the surface of the skin. This formed a hard, dense layer, measuring from 3 to 4 mm. in thickness. There was some hypertrophy of the smooth muscle fibres of the skin. There were no extensive changes in the muscles, but here and there were areas of fibrous invasion very different to the normal structure.

Practically these are the changes which have been described by all authors who have written on the subject, but we do not know how far they are primary, or whether they are secondary to undiscovered lesions in the nervous system. We have no clue as yet to the essential nature of the disease. The analogy of myxœdema, to which scleroderma is the cutaneous antithesis, suggests that it may be caused by some alteration in an internal secretion, or some disturbance of that nice balance between the various internal secretions, and which plays such an important rôle in nutrition. The disturbances in pigmentation, as intense as any which we see, may depend on some adrenal inadequacy. The frequency with which the acute forms follow an infection is paralleled by the thyroid insufficiency and atrophy caused by myxœdema after a fever such as measles or scarlet fever. There are a few cases, as the one reported by Grünfeld, which suggest strongly thyroid disease, and in his case a cure followed the use of thyroidin, but it cannot be any simple inadequacy or more uniform results would follow this plan of treatment.

The view that scleroderma is due to a terminal endarteritis, which has been much advocated, has the anatomical basis of the widespread vascular changes which have been met with in every autopsy. Dinkler regards it as an interstitial inflammation consecutive to the arterial disease. Lewin and Heller and many others regard the disease as an angiotrophic neurosis depending upon unknown changes in the trophic centre. These are the three important theories which have been advanced, each one of which only serves to throw into stronger relief our real ignorance of the true pathology.

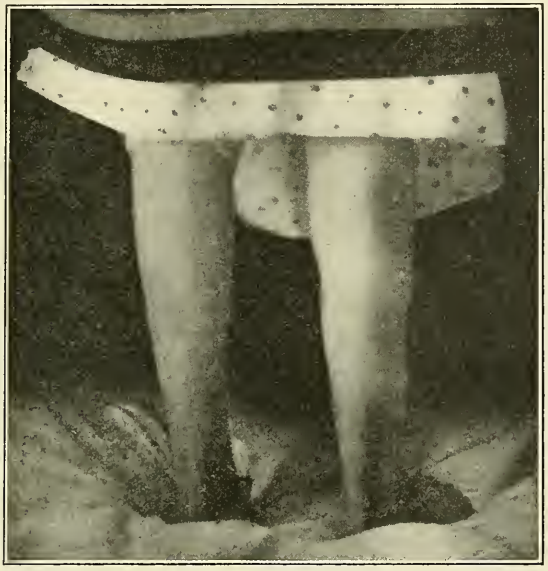
Distribution.—The face and extremities are most frequently involved. Of the 420 cases collected by Lewin and Heller, the upper extremities were attacked in 287, the trunk in 203, the head in 193, and the lower extremities in 122. In only 3 cases in my series was the face not involved. A universal scleroderma is rare, occurring only in 16 per cent. of the cases.

Symptoms.—There are three modes of onset—the simple atrophic, the œdematous, and the erythematous. The *atrophic* is the most common. Case X of my series illustrates it very well, and gives a good picture of the course of the disease in a severe case. S. G., aged forty years (seen with Dr. Julius Friedenwald), a healthy man, of good habits, began to notice in October, 1897, that his hands were a little stiff. In January, 1898, some of the nails festered at their bases, and his hands would get red and blue. In November his legs felt stiff, and he went to Hot Springs, Va. The feet became blue and swollen, so much so that he had to wear larger-sized shoes. He began to feel the cold very much. When I saw him in April, 1898, his face looked smooth, and the skin was everywhere firmer than normal. Both hands were congested, and felt firm and cold. There were scars at the roots of the nails and on the pads of several of the fingers. It was impossible to pick up the skin on the back of the hands. The feet were in the same state. The skin of the arms, legs, and trunk was not involved. He had lost thirty pounds in weight in six months. During the next four months the disease progressed rapidly, and by October 1 had involved the skin of the entire body. The movements of the limbs were much restricted, and, although looking natural, the skin was everywhere tense and firm. He had constant pains in the arms and legs; the nerves were not tender, nor were the joints swollen. The face was shrunken and mask-like, and he moved the lips with difficulty. The temperature was always about 101°, sometimes reaching to 103°. Through the winter he got progressively worse. The sclerosis of the skin of the trunk became extreme. He could move neither head nor limb, nor could arm or leg be flexed. He could scarcely open his mouth, and the face had become mummified. He wasted rapidly, and the whole body was as rigid and stiff as a statue. The back became bowed, so that the trunk could not be extended. He had recurring attacks of diarrhœa of great severity. During the last months this poor man presented an appalling picture—literally a breathing mummy. He retained his intelligence until near the end, which came March 14, 1899, less than two years from the onset of the disease. In two other cases which showed this atrophic type from the onset there was extreme pigmentation.

In only one case in my series was the onset with *œdema*, in the midst of which were depressed areas compared by Erasmus Wilson to the effect produced by pressing the finger into a bladder filled with lard.

The *erythematous onset* is of two types: in one, a diffuse erythema and swelling occur in the face or in parts of the trunk; in the other, the picture is that of the vasomotor disturbances of the hands and feet, like Raynaud's disease.

Fig. 77



Scleroderma with œdema, showing depressions.

In Case XV the erythema and swelling were more marked than in any other of the series. S. J., aged forty-seven years, a healthy man of good habits, was seen December 29, 1900, with Dr. Urban Smith. The trouble began three years before, with swelling of the face and of the left wrist and arm, and these parts would be at times so red that he had to remain at home. The hands became painful, and within the last year the skin of the chest has become red and swollen. When seen the face was smooth, without wrinkles, and the skin everywhere parchment-like. The entire neck was hidebound. Over the front of the chest the skin was reddened, a little darker than normal, and swollen. Toward both axillæ there was a distinct line of demarcation. In the upper part of the axillæ, and extending over the scapular regions, there were the same erythema and swelling. The hands were sclerotic and stiff. The anterior surface of both forearms was swollen and red. I followed this case for more than two years. The general sclerosis became more marked, and the hidebound condition was universal. The hands and feet became purple. I never saw more persistent or deeper cyanosis; it took more than thirty seconds to obliterate the anemia of a finger mark. Toward the end he had remarkable attacks of tachycardia. He died five years from the onset of the disease.

In several cases the onset was with symptoms suggestive of Raynaud's disease, so much so that in Cases XI, XVI, and XVII the diagnosis of this affection was made. In Case XVI, a woman, aged thirty-two years, the hands and fingers became swollen and red. "At times they were more blue than red, and again they would be perfectly white and cold. Usually all the fingers would be affected, but the middle right finger was the most frequently involved. The change in color to white, blue, and red occurred within a few hours. These attacks came on irregularly, at intervals of about a month." Could anything be more typical of the onset of Raynaud's disease? This patient had a most severe attack, with widespread involvement of the skin and the most extensive pigmentation, and death followed three and one-half years from the onset. In Case XVII, also a most severe, diffuse form, "he first noticed that the fingers and hands would become purple or almost blue; then at times they would be swollen and white. They were much worse in cold weather." In Case XI, a woman, aged twenty-eight years, the disease began with local asphyxia of the fingers and toes. As it was winter, she thought at first they were frostbitten. The pads of the fingers split open and were very sore, and the feet became so swollen and tender that she could not walk. In the summer she was better; then as the cold weather came on the hands and feet would ache, and, as she expressed it, she was "half crazy with the pain,," and at times the fingers and toes got so black that gangrene was feared. I saw her four years after the onset of these symptoms, and she then had well-marked features of scleroderma. The movements of the face were restricted, the nasolabial folds were obliterated, and the nose had become sharper. The skin, which could not be picked up, was hard and parchment-like. The hands and feet had a natural color, but they looked large and flabby. The middle finger of the right hand was cyanosed. The movements of the fingers were stiff, and she could not pick up small articles easily. The hands felt cold, and the skin was everywhere firm. The pads of the fingers were puckered and scarred. I saw this patient at intervals for nearly three years, and she had a very thorough treatment with thyroid extract, with decided benefit. For a time the face was worse, but the skin became softer and the hands were less stiff.

Several writers have called attention to the onset with arthritis, and in my series there were three cases in which this was a special feature. Thus, in Case XVII, following a severe attack of influenza in March, 1898, the joints began to be painful and stiff, and by June nearly every joint in the body felt sore, although there was neither swelling nor redness. In another case severe attacks of arthritis occurred at intervals for three or four years before the skin was affected.

In many cases the earliest stage is an œdema, with slight efflorescence, a firm, solid infiltration which does not pit. The appearance is not unlike the erythema of leprosy. It may be diffuse, or in small patches, and in Case XIII of my series there were raised spots not unlike erythema nodosum. It may last for weeks or months. Then the skin begins to get hard and tense, the stage of induration, and the color changes to a dead white, or it has the tint of old marble or of parchment. The

consistency changes, and it feels firm like a bit of frozen skin, and it may be impossible to pick up a fold. This is a very characteristic test, as everywhere, even in the fingers, the normal skin can be picked up in folds. In some cases there is not a bit of skin that can be pinched between the finger and thumb. The folds are obliterated, the wrinkles disappear, and the face has a mask-like aspect—Gorgonized. The face grows smaller, the lips thin, the nose pointed and narrow, the cheeks smooth, the ears shrunken, the eyes expressionless, and the diagnosis may be made at a glance. The hands look smooth, the fingers are semi-flexed, the terminal joints may be shrunken and involved in a sclero-dactylism of the most advanced type. The hands are converted into rigid, immobile organs. In severe cases the unfortunate victim is as though he had been put in the fabled shirt of Nessus, which had gradually contracted upon him. The back is rigid, the neck is fixed, and he may resemble a frozen corpse or a mummy, without the power of motion, save in eyes and tongue, which alone give witness to remaining life.

As the disease progresses three changes occur: (1) *Atrophy* follows the induration and the skin becomes thinner, although not softer. At the lines of extension this gives a ridge in which three zones may sometimes be seen: an inner, yellowish brown, corresponding to the atrophic portion; a white, indurated portion; and beyond it a narrow zone of erythema. In the gradual extension, weeks or months may elapse before a distance of an inch is covered. In other cases, by the coalescence of contiguous areas, large portions of the skin may be involved. The atrophied skin may gradually grow more natural looking and softer. (2) The second change is in the involvement of the *subcutaneous tissues* which become sclerotic and bind the skin tightly to the subjacent part. The mobility of the skin is in this way lost, and it can no longer be moved freely upon the muscles or bones. When atrophic and smooth the skin may fit on the bones of the hand like a glove. (3) And the third change is in the *color*, most frequently an increase in the pigmentation, giving to the skin a parchment-brown appearance. My series afforded most interesting studies in this change, which I have dwelt upon fully in my paper.[1] There may be the muddy brown discoloration which is common in the atrophic areas, or there may be a curious mottled or freckled appearance, such as we see so often in the arsenical pigmentation about the abdomen. But the most remarkable instances are those in which the entire skin becomes of a deep brownish black, like the most extreme form of Addison's disease. In Cases VIII and XVI the diagnosis of suprarenal disease was suggested, and I do not know that there is any other condition in which we meet with a more intense melanoderma.

Atrophy of the pigment, causing areas of leukoderma, almost always accompanies the pigmentation. They are well shown in the colored plate illustrating my paper. In the midst of almost black areas there may be scattered patches of normal-looking or dead white skin. On the abdomen the alternation of lines with hypertrophy and atrophy of the pigment may present a very curious appearance. In Case IX the inner aspects of the

[1] *Journal of Genito-urinary and Skin Diseases*, New York, 1898.

thighs and the popliteal spaces were very dark—in fact, as black as the skin of a negro. This had come on gradually, as the disease had extended. In the atrophic areas the pigmentation became very intense, but within two years it had changed to a light brown, and here and there were a few spots of leukoderma. In none of my cases was there pigmentation of the mucous membranes. An interesting change in the sclerotic skin is the development of telangiectases, very similar in appearance to those which appear in the *x*-ray scars.

The secretory functions of the skin may be undisturbed. In several of my patients there was hyperidrosis, and the skin of the hands and feet was always moist. When touched, the hard, cold, clammy sensation of the sclerodermatous hand feels like that of a corpse. There is no special change in the secretion of the sebaceous glands. The skin is not often dry and scaly.

Trophic changes other than the scleroderma itself are not uncommon. Several of my patients had local suppuration about the nails, and in Lewin and Heller's collection there were forty-eight with *ulcers* about the fingers or knuckles. They have occurred in my series either in the early stages in connection with the vasomotor changes, or late when the knuckles and finger-joints were hidebound. Sclerodactylism is a not uncommon event, occurring in three of my eighteen cases. It comes on gradually with or without previous local asphyxia and trophic changes in the pads of the fingers. In Case II, at the end of the fifth year both hands presented a typical condition of sclerodactylism; he could not make a fist, the motion at the metacarpophalangeal joints was very slight, and there was complete immobility of the first and second joints of the fingers; the thumbs could be opposed to the first and second fingers, so that he could still use his hands to dress and undress himself. The fingers were bent and the terminal phalanges at right angles to the others. There was a gradual wasting of the end-joints, which were thin, pointed, and about half the length of an ordinary phalanx. The nails were curved, ribbed, and shortened. There were scars all over the finger-joints, and on the knuckles there had been troublesome open sores.

The *hair* may fall out from the sclerotic skin or get very thin, and this seems the usual course; in a few cases with the pigmentation there is an increase in the growth of the hair, as is very well shown in the colored plate illustrating my paper. Loss of the pigment of the hair has been observed.

Trophic changes may occur in the deeper parts. The *bones* may be affected, and, as in Case XIV of my series, all those of the left upper extremity, including the scapula, were atrophic. More often the change is confined to the fingers. In a few cases local hypertrophy of bone has been observed, thickening of the tibiæ or of the malar bones. The *muscles* beneath the sclerosed skin may be involved. The deltoid and anterior group of muscles of the forearm were hard and fibroid in Case XIV. Muscle atrophy has been described in connection with sclerotic changes in the skin covering it; in other instances the muscle has been sclerotic beneath a normal skin. A widespread myositis has been met

with in connection with scleroderma of the thorax and nates (Kaposi). Calcareous nodules may form beneath the skin. The widespread interstitial and subcutaneous calcinosis may be mistaken for scleroderma.

How far the *joint troubles* of the disease represent an arthropathy is a question. They are common, particularly in the early stage. There may be pains alone, and disability from this cause. In one of my cases there was inflammation of the right ankle for weeks before the onset of the scleroderma in the hands. Deformity and osteophytes have been met with, but, as a rule, it is a painful arthritis of onset. Subsequently the joints become fixed by the sclerotic skin, and toward the close not a single joint of the body is mobile. In the postmortem in Case X no changes were found in the joints.

Changes in *sensation* are not common; numbness and tingling may be present, but there is not often pain, except when the disease begins with the features of Raynaud's disease. Case XVI had severe pains in the hands and feet. As a rule, scleroderma is a painless affection and sensation is well preserved, even in the atrophic skin. In the early stages, as was well marked in Case XIII, the acuteness of the sensation was duller in the affected areas. There may be great sensitiveness to cold, and, as a rule, the patients are more comfortable in summer.

The general health may remain very good. Case II, Levi B., came back year after year to the clinic, and although his face, hands, and legs were affected, he was very comfortable, and could even dress himself. The erosions over the knuckles gave him the most trouble. In the severe cases a cachexia comes on, the patient gets thin, there is fever, diarrhœa, and death follows from exhaustion. One of my patients died suddenly, another from pneumonia. Fever is not a constant feature: as the sclerosis progresses actively there may be a degree or more, but, as a rule, the course is afebrile. The pulse is usually unaffected. In two of my cases there were attacks of tachycardia. Arteriosclerosis may be present, but there may be extreme scleroderma without much, if any, change in the arteries. No special changes have been met with in the heart.

Blood examinations were made in eight or ten of my cases. There were no special alterations. In Case XVI the leukocytes were 10,500 per cmm., the eosinophiles 3.3 per cent., and the small mononuclears 19 per cent. In Case XVII the eosinophiles were 2.4 per cent.

The urine is, as a rule, normal. Albuminuria is present in a few cases; sugar has been detected.

Association with Other Diseases.—A number of cases have been reported of scleroderma in Graves' disease. One patient in my series presented a typical instance of this combination. It is usually of the legs, and not often generalized. Thyroid enlargement has been present in a few cases, and the association with atrophy has been noted.

One of the greatest difficulties is in the association with Raynaud's disease—whether the scleroderma begins as a complication of this affection or whether the local asphyxia and trophic changes may be regarded as part of the scleroderma. In five of my cases the vasomotor changes were most marked; in two the symptoms of onset were those of Ray-

naud's disease. The case reported under modes of onset is most typical, and Case VI presented very similar symptoms. In none of the cases did the asphyxia pass on to severe gangrene, although there were superficial losses of substance. The vasomotor changes in the disease are extraordinary. In Case VII there was the most remarkable vasomotor ataxia I have ever seen—the cyanosis of the legs when he stood up was most extreme—they became plum-colored in half a minute; when on his back and the legs held up the skin at once became anemic. One could literally see the blood fall into the legs when he stood up.

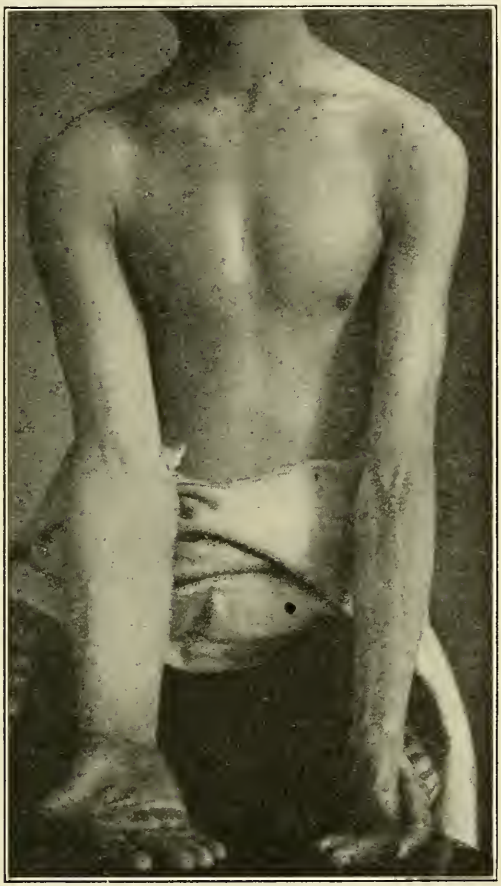
Cassirer makes a good division of the cases with these marked vasomotor phenomena: First, instances of Raynaud's disease, in which in the late stages, besides the gangrene, there are trophic changes in the skin of the fingers and hands, which become smooth, glossy, and hard; the fingers may be immobile, and a well-marked state of sclerodactylism is produced. The process is limited to those parts which have been frequently the subject of attacks, and there is no extension to the arms or legs or trunk. Secondly, cases in which the scene opens with marked vasomotor changes—local syncope and asphyxia, and acroparesthesia. Gradually, without progressing to local gangrene, these symptoms are succeeded by a typical scleroderma, which is not limited to the parts which have been affected with these vasomotor changes, but extends widely. Thirdly, there are the rare cases in which in a typical sclerodermic case Raynaud's symptoms supervene with gangrene.

Local Panatrophy in Scleroderma.—In Case XIV the entire left arm was atrophic and the skin sclerosed; some of the muscles were firm and hard. Fig. 78 shows the condition very well. The condition was very like the local panatrophy described by Gowers and by Harry Campbell. In Gowers' case, a woman, aged thirty-three years, "presented in certain areas of the trunk, limbs, and face areas of wasting of all the subcutaneous tissues down to the bone with thinning and discoloration of the skin. They were irregularly distributed without apparent relation to muscles or to nerve distribution." One patient, aged thirty-two years, had atrophy about the shoulder, with wasting of the skin and involvement of the subcutaneous tissues and muscles, and in one place the bone also was atrophied.

Course and Prognosis.—There are acute and chronic forms. The acute cases are usually in children, and have followed an infection. In the *Archiv f. Dermatologie*, 1900, Band li, Müller reports a case in a girl, aged sixteen years, coming on six weeks after otitis media. In three days the arms, cheek, back, and neck were as hard as wood, and the head was immobile. The skin could not be pinched up. The face was only slightly involved. There was no disturbance of sensation. The affected regions were tender to the touch. In Marsh's case, a two-year-old child, the acute onset followed diphtheria, and within two weeks the hands and face and trunk were involved. Some of these cases have subsequently had a chronic course. In the most rapid case in my series, No. X, death occurred within two years. As a rule, the course is very chronic. Lewin and Heller found ten cases in which the disease had lasted more than fifteen years; one of these had a duration of forty-eight years, another

of thirty. The longest case in my series, Levi Bear, well known to so many of the graduates of the Johns Hopkins Medical School, had the trouble for more than fifteen years. The disease became stationary after about five years' duration.

Fig. 78



Scleroderma with local panatrophy of the left arm.

The arrest may leave the victims in the stage when they are fairly comfortable, or there may be great disability. In no instance in the series did complete cure take place—an experience which does not bear out the hopeful view of some dermatologists, Crocker, for example, who said, "The disease, as a rule, tends to get well spontaneously." Lewin and Heller give 16 per cent. of recoveries. The outlook in children is better even in the acute cases; the percentage here in the statistics of these authors is 31. Recovery has followed in a month or six weeks. The cachexia carries off a majority of the patients; others died of bronchial, renal, or pulmonary complications. Death may occur suddenly.

Diagnosis.—Dermatologists recognize two forms of the disease—a local, often called morphœa, and the general or diffuse. Hutchinson made an interesting classification of the cases—an *herpetiform*, which, like herpes zoster, is distributed in bands and streaks, and may be bilateral; an *acroteric*, beginning in the extremities with symptoms like Raynaud's disease, and leading to acroscleroderma; and lastly, a *generalized* scleroderma, a hidebound condition of the skin. The local disease presents identical anatomical characters, but there are certain differences—it often follows nerves, distributed accurately in their course. Lewin and Heller have collected many cases illustrating this. In a patient of Brissaud's the sclerotic bands corresponded accurately to the seventh and eighth cervical segments, the first and second dorsal, the fifth lumbar, and the first sacral segments. There is a much greater tendency to complete recovery; pigmentary anomalies are not so common; and sclerodactylism does not occur. The local form may occur on arm, leg, or trunk, less often in the face. It begins in the manner already described, and only the limitation in area separates it from the more severe form. A case may start in one or two spots, and gradually spread and become diffuse.

The diagnosis is rarely in doubt. In not one of the cases in my series was there any difficulty in recognizing the existence of scleroderma, but in two the question arose of the coexistence of Raynaud's disease, a point which has been discussed. The sclerodactylism may suggest syringomyelia, but the absence of sensory and other changes is sufficient to differentiate the two conditions.

The local panatrophy of Gowers resembles scleroderma, and some of the cases may be this disease. Only in the early stages do the cases offer any difficulty. The preliminary erythema and infiltration may strongly suggest leprosy. A point of moment is that the sclerodermatous erythema is never extensive for a long period without the other changes; the hard œdema begins to disappear in places and the skin atrophies and changes in color. On the whole, generalized scleroderma is a disease easy of recognition. A glance at the face of the hands may suffice; difficulties only rise in a few rare instances when the vasomotor disturbances are extreme and when the local asphyxia leads to changes suggestive of Raynaud's disease.

Treatment.—I doubt if any remedy has an influence on the course of the disease, unless it be the *x*-rays, which should be given a thorough trial. In the acute cases hot baths and massage should be tried, and in all forms systematic hydrotherapy should be used. Massage is helpful, and in any case keeps the skin softer and promotes nutrition. These measures with electrical treatment should be carried out thoroughly as early in the course as possible. A stay at one of the baths (alkaline and sulphur baths), should be advised. Of remedies, I have given a very thorough trial to nearly all on the list, the iodides, salol, and the salicylate preparations, and the various thyroid preparations. In my paper describing the first eight cases of my series, I give the details of six cases treated with thyroid extract. Of the remaining ten cases, nearly all received a full trial of this remedy. Possibly to it the arrest in three

or four of the cases may be attributed, but in Case X the disease made rapid progress under its use; and the best that can be said is that in some cases it appears to retard the progress. The remedy is well borne for years in doses of gr. v of the extract three times a day. I saw no ill result. In neither of the cases in which tachycardia occurred was this due to the thyroid. It is well to omit the use for a week or ten days at the end of each period of six or eight weeks. Various other thyroid preparations were tried without any special effects: Thymus extract, adrenalin, suprarenal extract, and cœliacin (mesenteric gland extract). Fibrolysin has been used without benefit.

ERYTHROMELALGIA (WEIR MITCHELL'S DISEASE).

Definition.—"A chronic disease in which a part or parts of the body, usually one or more of the extremities, suffer with pain, flushing, and local fever, made far worse if the parts hang down" (Weir Mitchell).

Introduction.—In 1872 Weir Mitchell described in the *Philadelphia Medical Times,* under the title "On a Rare Vasomotor Neurosis of the Extremities," a peculiar red neuralgia. In 1878, in the *American Journal of the Medical Sciences,* he still further elaborated his views on the subject. Other papers by him are to be found in the *Medical News,* 1893, and the *American Journal of the Medical Sciences,* 1899 (with Spiller). He gave to the condition the name erythromelalgia, signifying a painful red state of a limb. Cases had previously been described by Graves, Paget, and others. The literature is very fully given in Cassirer's monograph (*Die Vasomotorisch-trophischen Neurosen,* Berlin, 1912) and in the *Index Catalogue,* Series II. Much discussion has taken place as to the existence of erythromelalgia as a separate disease, apart from Raynaud's disease, affections of the spinal cord, obliterative endarteritis, and the various forms of peripheral neuritis, in all of which pain and redness of the extremities may occur. These conditions should, I believe, be excluded, and the name limited to a vasomotor neurosis with the features above given, a small but perfectly definite group of cases.

Etiology.—The disease is rare. I have seen only one case in private practice in which the diagnosis seemed clear. At the Johns Hopkins Hospital in twenty years (to 1909) there were three cases. Cassirer collected 90 observations which have been reported as erythromelalgia, but a great majority of these belong to other conditions.

Age and Sex.—Men are more subject to the disease than women—46 to 32 in Cassirer's figures. His age table is: from one to ten, 2 cases; eleven to twenty, 2; twenty-one to thirty, 21; thirty-one to forty, 13; forty-one to fifty, 11; fifty to sixty, 12; sixty to seventy, 2; above seventy, 2. Graves' case was in a woman aged eighty-two years; Henoch's in a teething child.

Among *predisposing causes,* puberty, menstrual disturbance, and the climacteric are mentioned. In a few cases the disease has followed an infection—rheumatic fever, gonorrhœa, syphilis. Cold and damp are important *exciting causes.* Weir Mitchell's first case was a sailor who

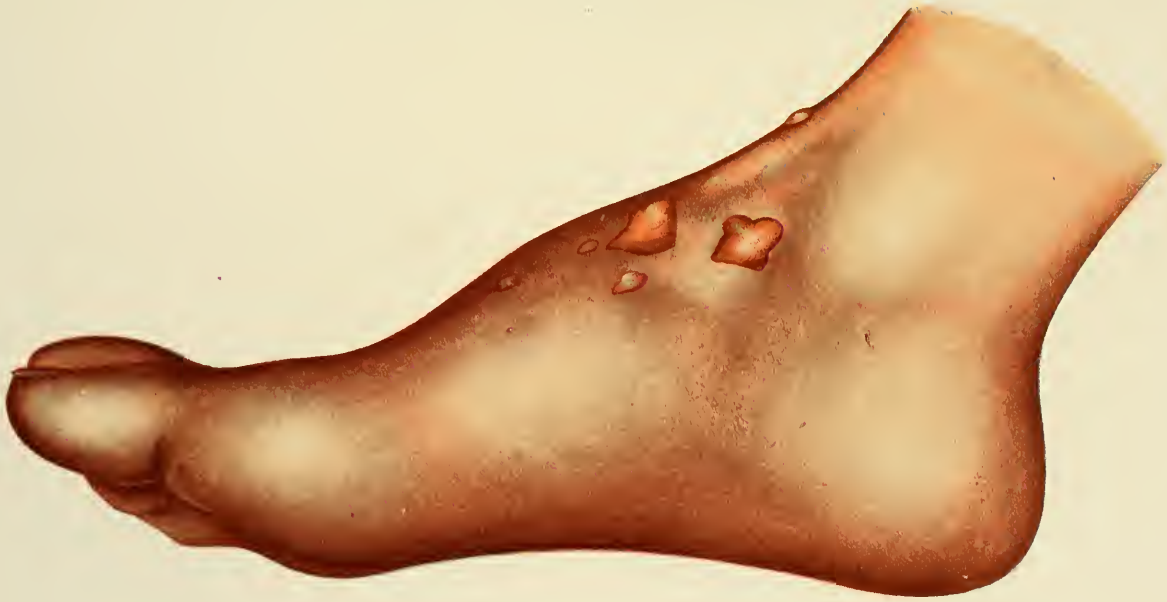
had been much exposed; Elsner's patient had had to do a great deal of washing; Paget's patient was much given to cold douches and hydrotherapy, standing with the feet in cold water. In several cases the disease has come on after exposure. In my case the girl got her feet wet and had to sit for some hours without changing. Overexertion or a sudden strain has been an important factor—overuse of a hammer, prolonged use of the legs in working a sewing machine, or a protracted march. In a few cases a blow or an injury to the limb has preceded the onset of the symptoms. Several cases have been in highly strung neuropathic individuals.

Pathology.—Cassirer recognizes two groups of cases of erythromelalgia —one in which the symptoms are localized in a definite nerve territory, the other in which they are distributed over the distal portion of a limb. The first group has many points of resemblance to neuritis, but may exist without the positive signs of neuritis, anesthesia or other disturbance of sensation, disturbance of motion, or painful points along the course of the nerve. In the second group no basis exists for the diagnosis of any special lesion, arterial, neuritic, spinal, or cerebral; although from the distribution and general features we may suppose that in the one the trouble is peripheral, in the other central. This is about as far as our knowledge goes of the pathology of erythromelalgia, and it is not very far! The postmortem reports are not in accord: "Once changes were found in the peripheral nerves (Weir Mitchell and Spiller); once changes in the posterior roots (Auerbach); in three cases the peripheral nerves were intact (Weir Mitchell, Dehio); the arteries were found diseased in three cases (Sachs and Wiener, Dehio, Weir Mitchell and Spiller)." Cassirer thus summarized the results. It is very probable that the cases with local distribution are due to changes in the peripheral nerves; the symptoms resemble closely those caused by certain forms of peripheral neuritis. When the whole limb is involved the vasomotor centres are probably at fault, but what the nature of the change and where, we have at present no clue. The pathology will be found to be much the same as that of Raynaud's disease, with which erythromelalgia has very close affinities.

A more careful study of the nerve centres in cases of spinal cord and cerbral lesions associated with a congested and painful state of one or more extremities may throw some light on this dark chapter in neurology. The arterial cases should be cut out of the category altogether, as forming a separate and remarkable malady (with which we may well honor the memory of a good pathologist by associating the name of Friedländer) worthy of the most careful study. The researches of Erb and others have shown how common are these cases of endarteritis of the vessels of the extremities, and how diversified are the symptoms; one group has a striking similarity to the condition under consideration.

Symptoms.—Redness, pain, and swelling are the cardinal features of the disease. A very bright, healthy-looking girl, aged about twenty years, walked into my consulting room on crutches. When she removed the felt shoe and stocking from the left leg it was seen to be swollen and red, as high as the middle of the tibia. The toes were a little blue,

PLATE XXIV



Erythromelalgia. Foot after hanging down for twenty minutes.

(Case of Dr. J M. Taylor.)

PLATE XXV

Erythromelalgia. Foot after hanging down for thirty minutes

(Case of Dr. J. M. Taylor.)

but in a few minutes, as she rested on the sofa, they, too, had the vivid pink appearance of the foot and leg. The swelling was moderate and most evident about the ankle and tarsus. When she sat up and hung the foot down the redness became more marked, and the toes again became livid. If she attempted to put the foot to the ground she winced, and said it hurt very much, but on insisting she stood alone on the foot, but the pain increased and was chiefly in the sole and in the toes. In the recumbent posture the color was less intense and the pain ceased. When the foot was elevated the redness almost disappeared, but not entirely from the toes. To the touch the leg and foot were hot, and the temperature was 6° higher than on the corresponding parts of the other leg, much less than the hand suggested. It was nowhere painful on pressure, except at one or two spots in the sole, the worst near the heel and at the ball of the big toe. There was no pitting. The pulsation in the arteries was much fuller and more evident than in the sound leg. There was no tenderness along the course of the nerves. The veins were not visible except on the dorsum of the foot. In every other respect the girl was healthy. About three months previous she had got her feet wet, and had to sit for several hours without changing. In a few days she began to feel pain in the sole and toes of the left foot, but only when walking. Then she noticed the toes were of a bright-red color. The condition has gradually grown worse, and extended first to the whole foot and now half-way up the leg. She has very little pain except when she puts the foot to the ground, or if it has hung down for a long time. She is not disturbed at night, and her general health is excellent. Careful bandaging, rest, massage, and hydrotherapy were advised, but months passed without much change; then for no very obvious reason the condition began to improve, and about a year after I saw her she wrote that she was practically well.

Among the score or more of cases of painful red extremities that I have seen due to various causes—organic lesions of the spinal cord, endarteritis, neuritis, and Raynaud's disease—this case stands out as the only one in which the diagnosis of erythromelalgia seemed justified.

Parts Affected.—The feet are most often involved. In Cassirer's analysis the involvement was: both feet, 20 cases; one foot, 7; both hands, 10; one hand, 3; all four extremities, 13; and hand and foot of the same side, 2. In 12 cases the pain and redness were limited to the distribution of a single nerve. The fingers and toes are usually involved first, and the trouble spreads upward, and may cause swelling of the lower leg or of the forearm. It rarely reaches above the elbow or knee, but the pain may extend to the hip or the shoulder. One or two toes may be affected for weeks or months before the disease extends, or the trouble may begin in the sole of the foot or the palm of the hand. After persisting for months or for a year or more in one foot it may extend to the other. In marked contrast to Raynaud's disease, the ears and nose are not affected. In a few cases painful red spots have appeared in other parts of the body, and Mitchell remarks that he has seen this distribution and suggests, indeed, that similar vasomotor disturbances may occur in the muscles and bowels. I have seen no case reported with abdominal

colic, such as is so common in angioneurotic œdema, and occasionally in Raynaud's disease.

The most striking objective feature of a case is the *redness*, which in typical instances is the color due to an active hyperemia—a deep pink or violet-red, diffuse, not mottled, and sometimes sharply limited above. The veins may be swollen, but the general appearance is that of an inflammatory congestion, not of a venous stasis. One of the most remarkable features upon which Weir Mitchell laid great stress is the influence of change of posture; when the foot hangs down the congestion increases at once; when placed above the level of the patient's body, as he is recumbent, it grows pale, and the congestion may almost completely disappear. Not that this is peculiar in any way to erythromelalgia, but one does not often see it in the acute hyperemia. In the cold and in long-standing cases there may be blueness or asphyxia, but this is rare. The temperature is always higher, 4° to 6° or more, less than the hand suggests, as the affected part feels hot and the arteries of the foot may be felt to throb. *Pain* is almost always present, either an intense burning sensation or a sharp, stabbing sensation of a less continuous character. When at rest there may be nothing more than an unpleasant hot feeling, but on movement, as in attempting to put the foot to the ground, the pain may be severe. The slightest pressure with the finger may cause pain. Very rarely is the pain of the maximum intensity seen in Raynaud's disease. *Sweating* is a common feature, and it may be hyperidrosis. Thickening of the skin, pigmentation, and changes in the nails may occur. More or less swelling is almost always present, but there is no pitting on pressure. Disturbances of sensation are not common, but there may be hyperesthesia or pain along the course of the nerves. *Atrophy* of the muscles of the affected part may occur, as in the small muscles of the hand or foot; occasionally, as in one of Mitchell's cases, the muscles of the affected leg may waste. In the protracted cases there is always some wasting from disease. Serious trophic changes leading to gangrene do not occur. The cases that have been described belong to the category of Raynaud's disease, or are due to obliterative endarteritis, and it may be very difficult to say in a given case which condition is actually present.

Diagnosis.—There are four chief conditions in which "pain, flushing, and local fever," to use Weir Mitchell's words, occur, and which may be confounded with erythromelalgia, or which may simulate it so closely that it will depend altogether on the conception one has of the disease where an individual case is placed. I would limit the term to a small but well-defined group conforming clinically to Weir Mitchell's original description, and of which at present we do not know the anatomical basis. A "red, painful neuralgia" of an extremity may be associated with Raynaud's disease, with certain affections of the spinal cord, with endarteritis obliterans (Friedländer's disease), and with peripheral neuritis.

Raynaud's Disease.—Many cases simulate closely erythromelalgia, in others the two conditions appear to have been associated, or the one may pass into the other. Objectively, every case of Raynaud's disease becomes one of erythromelalgia in the stage of active hyperemia, when the part is

red and hot and painful, and yet typical cases have features which suffice to separate the two diseases, although it must be confessed by a very thin partition. Weir Mitchell's differential table may be given:

Raynaud's Disease.	Erythromelalgia.
1. Sex—four-fifths females.	1. In 22 cases 2 were women.
2. Begins with ischemia.	2. Little or no difference in color is seen until the foot hangs down in upright position, when it becomes rose-red.
3. Affected part becomes bloodless and white. In certain cases there is a deep, dusky congestion of a cyanosed part with or without grangrene.	3. The arteries throb and the color becomes dusky red or violaceous in tint.
4. Pain may be absent or acute, and comes and goes; has no relation to posture; may precede local asphyxia.	4. Pain usually present; worse when the part hangs down or is pressed upon. In bad cases more or less at all times.
5. Unaffected by seasons. In many cases all the symptoms are brought on by cold.	5. Worse in summer, and made worse by heat; eased by cold.
6. Anesthesia to touch.	6. Sensations of all kinds preserved.
7. Analgesia.	7. Hyperalgesia.
8. Temperature much lowered and unaltered by position.	8. Temperature above normal. Dependency causes in some instances an increase, in others a lowering of the temperature.
9. Gangrene local and limited, and likely to be symmetrical.	9. No gangrene; lesion asymmetrical.

Affections of the Brain and Spinal Cord.—I have already spoken of the vasomotor and trophic changes simulating Raynaud's disease, which are met with in organic diseases of the spinal cord. A condition of painful erythema, with swelling, may occur, and many cases have been described as erythromelalgia. In hemiplegia the forearm and hand may become red, painful, and swollen, a vasomotor change very like Weir Mitchell's disease, and the condition may persist for months. I saw a hemiplegic whose hand and arm had been painful and the hand red and œdematous for more than six months; and at the Infirmary for Nervous Diseases, Philadelphia, I had a patient whose sufferings from this cause were severe. A number of cases have been reported in locomotor ataxia, and Collier recorded five instances in multiple sclerosis. Altogether, Cassirer has collected 22 cases in this group. The clinical picture is often a vasomotor paresis, as in the hemiplegic arm, but it may resemble Weir Mitchell's disease very closely. It is very difficult to say just where these cases should be placed. Some of them simulate erythromelalgia closely, others are more like Raynaud's disease, and others again have a dull, dusky congestion, with swelling. They belong to a very definite group of vasomotor disturbances in organic lesions of the brain and cord, and I feel that it is better not to group them with erythromelalgia, however much the features may simulate this disease.

Endarteritis Obliterans.—Pain, redness, and swelling are common symptoms in one or both feet in Friedländer's disease—the progressive sclerosis of the arteries of the legs. The pain may be most severe and persistent. The color is often less marked than in the case here mentioned, and a preliminary spasm of the vessels may cause ischemia.

The arteries are not always obliterated. As Erb[1] pointed out, these cases are very common, and while they occur, as a rule, in elderly people, this group of symptoms may be met with in young or middle-aged men, the subject of syphilitic or other forms of endarteritis (Parkes-Weber). Three features distinguish these cases from true erythromelalgia—the presence of arterial changes, the tendency to gangrene, and the occurrence of intermittent claudication. Minor points are the greater liability to asphyxia and the great variability of the pain. There are cases without any disturbance of sensation, particularly in diabetes.

Neuritis.—A "red neuralgia" is often the best description of a local neuritis. I have seen two cases in which a neuritis of the arm caused a condition very similar to erythromelalgia. The other condition is pressure on the brachial plexus. In connection with Raynaud's disease, reference was made to cases described as due to tumors pressing upon the cauda equina or the lumbar nerves. In a woman, aged forty-three years, with secondary carcinoma of the supraclavicular and axillary glands, the fingers became numb and painful, then a vivid redness spread over the whole hand, and gradually extended to the middle of the forearm. There was little or no swelling, and no sign of venous obstruction. The pains in the arm, particularly along the inner side, became very intense, and for weeks the picture was that of an acute erythromelalgia. As the tumors increased there was pressure in the veins and great swelling of the arm and hand.

The alcoholic polyneuritis may be associated with marked vasomotor changes, rarely the active hyperemia, more often an extreme passive congestion, particularly when the limb hangs down. In a number of cases described as erythromelalgia the pain and redness have been in the course of individual nerves, the posterior tibial, the right internal plantar, the median, or the ulnar. It is by no means easy to say in these cases whether an actual neuritis exists, but we know that with inflammation of a nerve very severe pain and redness may occur. A nurse in the fourth week of a severe typhoid fever began to have pains in the front of the left arm, and in a few days there was a definite swelling between the elbow and wrist, with redness extending to the latter and severe pains on movement or when the parts were touched. The fingers were not involved. The post-typhoid neuritis is usually a motor affair without much pain, but occasionally there are marked vasomotor features, redness, swelling, and pain.

Under Raynaud's disease the question of scleroderma has been sufficiently discussed. It would not be possible, I think, to mistake erythema exudativum multiforme for erythromelalgia, or any of the forms of acroparesthesia or of podalgia.

Treatment.—An obstinate chronic affection, very resistant to all forms of treatment; such is the universal judgment of writers. It is best to carry out a systematic plan of treatment. Rest of the parts relieves the congestion and allays the pain, but not in all instances, as the redness

[1] It is a mistake to call intermittent claudication and endarteritis *Erb's disease* as Cassirer does. The condition was well recognized in man and horses years before Erb's admirable paper, which only served to call our attention to its frequency.

may disappear without the pain. The rest should be protracted for six weeks or, if necessary, three months. Massage, daily if it can be borne, very gently at first and afterward more vigorously. Many patients prefer cold, and some form of hydrotherapy may be tried, either cold packs or douches, or, if grateful, a local steam bath. Radiant heat should be given a thorough trial. The procedure suggested by Cushing, mentioned under Raynaud's disease, should prove helpful. Various forms of electrical treatment have been advised, and may be used. Locally and internally the resources of the pharmacopœia may be taxed to the uttermost without much relief. It is best, if possible, to avoid the more powerful narcotics, as morphine. In the local form, where the pain is limited to a single nerve territory, section or excision of part of the nerve may be practised.

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